Quantifying Efficiency in the Field of Injury, Mental Healthcare and Prevention

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Quantifying Efficiency in the Field of Injury, Mental Healthcare and Prevention

Het kwantificeren van efficiëntie op het gebied van letsel, geestelijke gezondheidszorg en preventie

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CHAPTER 1

General introduction

General introduction

New medical technologies and the ageing population have led to an increase in healthcare costs. Between 1999 and 2012, the healthcare costs in the Netherlands have increased by 6% annually (1). In these years, 10-14% of the gross national product was spent on healthcare (1). The estimated healthcare costs in 2015 were 85 billion in the Netherlands, which were mostly spent on hospital care and the treatment of mental disorders and cardiovascular diseases (1, 2).

The resources in healthcare are limited. For this reason, it is essential that policy makers reimburse treatment options that maximize health gain at the lowest possible costs. Consequently, choices between treatment alternatives have to be made. Health Technology Assessment (HTA) is a research field that is concerned with informing policy makers about these choices in healthcare. The term HTA refers to the systematic evaluation of properties, effects, and impact of health technologies (3). Policy makers need to consider the effectiveness of treatment alternatives, but also the costs. It is even more important to understand how the effectiveness of treatments relate to the costs.

In cost-effectiveness research, a key element of HTA, both of these aspects are critically appraised (4). Costs and effects of two or more treatment options are compared to each other in a cost-effectiveness analysis (CEA) (4), which provides important input for policy decisions. CEAs are especially useful when choices must be made between multiple treatment options for one specific disease.

Every disease has its own symptoms, characteristics, and consequences. Chronic or recurrent health conditions such as depression or diabetes are associated with disability and costs spread over many years or even lifetime (5), whereas the disability and costs associated with injuries such as arm fractures and concussions are mostly limited to a shorter period. Some diseases impair ability to perform paid work temporarily or permanently, which may have a significant impact on the productivity costs (6). These characteristics should be considered in order to identify all relevant aspects of specific health conditions.

This thesis explores the utilization of HTA in the field of injury, mental healthcare and prevention with the aim of investigating the cost-effectiveness of interventions and the methodology of health-related quality of life (HRQOL) measurement in injury patients. Important concepts related to HTA, cost-effectiveness research, preventive interventions, mental disorders, and injuries will be introduced in this chapter. Furthermore, the research questions and the outline of this thesis will be presented.

Health Technology Assessment

HTA is a multidisciplinary process to evaluate the social, economic, organizational and ethical issues of a health intervention or health technology (3). In this definition, health technology must be interpreted broadly. It does not necessarily refer to innovative technologies, but also to existing treatment alternatives and preventive interventions. As mentioned earlier, informing policy decisions in healthcare is the main purpose of HTA, which encompasses multidisciplinary aspects (Figure 1).

This thesis covers multiple aspects of HTA. The main areas of interest are the costs and effects (outcome) of interventions for selected diseases, but the relation between these concepts (cost-effectiveness) is particularly discussed. Other topics of interest are epidemiology, policy recommendations, and HRQOL.

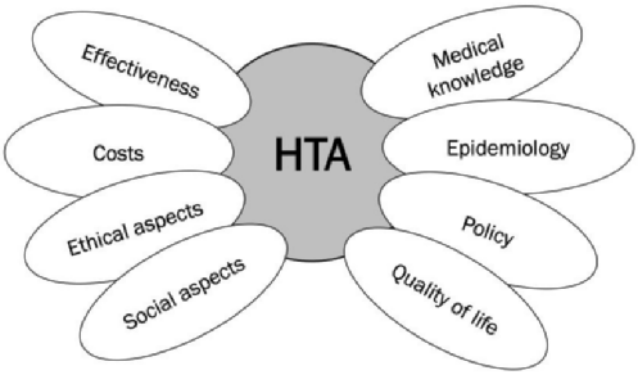

Figure 1: Aspects of health technology assessment (HTA) based on Habbema et al. (1989)

Cost-effectiveness

In a CEA, both costs and effects of two or more treatment options are compared by means of an incremental analysis (4) (Figure 2). In a strict sense, the term CEA does not refer to an incremental analysis, but this is necessary in order to make a comparison between treatment options. In practice, this usually means that a new treatment option is compared to the current standard treatment or usual care. In the incremental analysis, the difference in costs is divided by the difference in effects, which yields the incremental cost-effectiveness ratio (ICER) (4) (Figure 2). With this information, the relationship between costs and effects can be investigated in order to find the most desirable treatment option from a health-economic perspective.

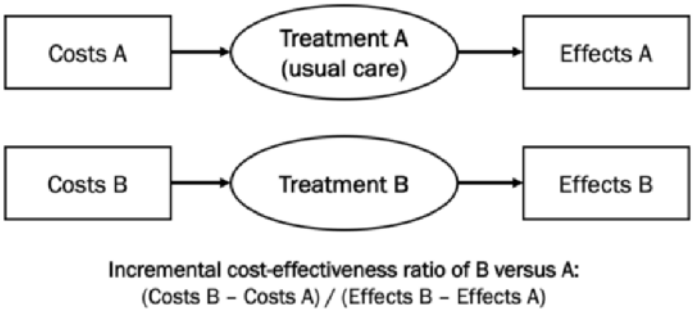

Figure 2: Cost-effectiveness analysis and incremental cost-effectiveness ratio (ICER)

Health-economic perspective

CEAs can be performed from different health-economic perspectives depending on the target audience and decision problem under evaluation. From a welfarist point of view, which regards health not merely as a goal, but also as a contributor to overall welfare, a CEA should consider not only healthcare costs, but also the financial consequences of changes in health (7). Given that health is intertwined with many facets of everyday life, such as work and social life, many of these consequences are located outside the healthcare sector. When a CEA is conducted from a societal perspective, all relevant costs and consequences are included irrespective of who pays or receives the benefits (7, 8). However, these costs and consequences outside the healthcare sector, even if they are relevant, are not always included in economic evaluations although health-economic guidelines recommend to do so (7, 9). The most commonly applied perspectives in CEAs is the healthcare perspective, which is limited to relevant costs and consequences within the healthcare sector (10).

Cost categories. Depending on the perspective of the CEA, different costs and cost categories are included in the analysis. The costs included in a CEA can be divided into four main groups: healthcare costs, patient and family costs, productivity costs, and other costs (4). Healthcare costs include treatment costs and all other medical costs such as prevention, diagnostics, hospital stays, and rehabilitation. Health problems are often associated with indirect costs for patients and their families. Examples of these costs are the use of supportive medical devices and travel costs for hospital visits. Other important costs are the costs due to productivity losses (6). Illness is often associated with reduced productivity, especially for patients with a chronic disease. Other costs consist of all costs in other relevant sectors, such as education or justice, which are also referred to as

intersectoral costs (7).

Interpretation of cost-effectiveness analysis results

Results of CEAs, expressed as ICERs, are generally presented in a cost-effectiveness plane, which provides a visual representation of the probability of an intervention being cost-effective in comparison with the control intervention (11). The incremental costs are usually displayed on the vertical axis and the incremental effects on the horizontal axis (Figure 3) (4, 11). When using the treatment alternatives A and B of Figure 2 as an example, the most favorable outcome would be that B is more effective at lower costs as compared to standard treatment A. In this case, the ICER is located in the lower right quadrant of the cost-effectiveness plane. The most unfavorable outcome is that B is less effective than A, but also more expensive. The ICER is then located in the upper left quadrant. Keeping the increasing use of costly new medical technologies in mind, it is often the case that the new intervention (B) is more effective than usual care (A), but also more expensive. In these cases, the ICER is located in the upper right quadrant.

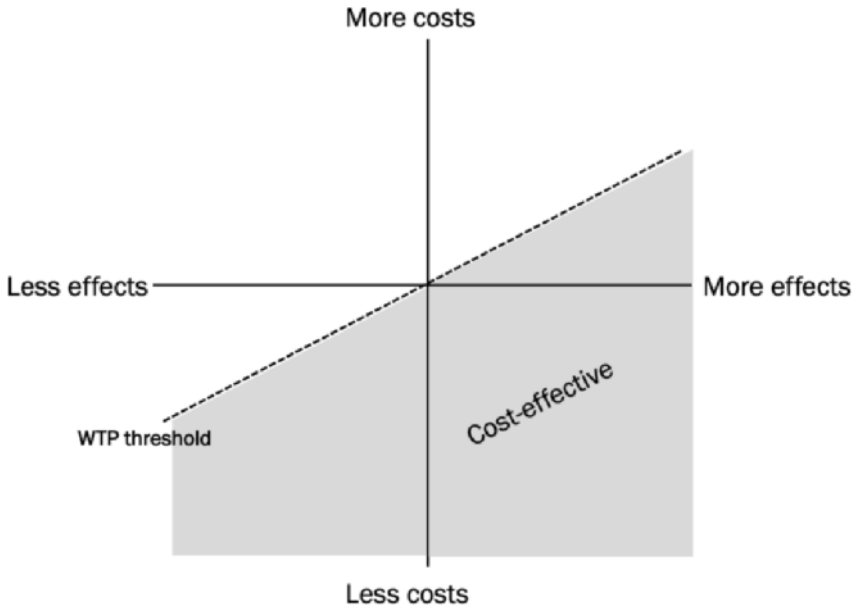

Figure 3: cost-effectiveness plane and willingness-to-pay (WTP) threshold

Willingness-to-pay. For ICERs located in the upper right quadrant, the cost-effectiveness of the intervention depends on the willingness-to-pay (WTP) for health gains. When an ICER is below the WTP threshold, the invention can be regarded as cost-effective. There is no international consensus on WTP thresholds as each country has its own healthcare system and economic situation. The National Health Care Institute (Zorginstituut Nederland), the Dutch governmental HTA agency, maintains a WTP threshold for a quality adjusted life-year (QALY) ranging between €20,000 and €80,000 depending on the disability weight of disease (Table 1) (12). In addition to this distinction in thresholds based on disability weights, the WTP threshold of €20,000 per QALY in the Netherlands is often used for preventive interventions, and higher thresholds (€50,000-€80,000 per QALY) for curative care (13, 14). In the United Kingdom, the National Institute for Health and Care Excellence (NICE) maintains WTP thresholds of £20,000-£30,000 (€22,900-€34,400 expressed in 2018 euros) (15).

Table 1: Willingness-to-pay thresholds and applications

Threshold per QALY	Disability weight [1]	Application
€20,000	0.1 – 0.4	Prevention [2]
€50,000	0.41 – 0.7	
€80,000	0.71 – 1	Curative care [2]

[1] based on National Health Care Institute (Zorginstituut Nederland) recommendations (12).
[2] based on van den Berg (14) and Smulders (13).

Outcome

Type of analysis

The outcome used in CEAs depends on the type of analysis. In health-economics, a CEA is a specific type of analysis but it is also used as an umbrella term for different types of CEAs. The scope of this thesis is limited to the three most frequently used types of CEAs (Table 2) which differ in the way the outcome of interventions is measured (4). In a CEA, regarded as a specific type of analysis, the outcome is measured in natural units of effects. Examples of outcomes are blood pressure measured in mmHg or the length of hospital stay measured in days. A QALY, a generic HRQOL measure, is the outcome in a cost-utility analysis (CUA). In a cost-benefit analysis (CBA) the outcome is expressed in monetary values by calculating the net monetary benefit (NMB) of the intervention and the comparator. For example, when the WTP for a QALY is defined, the NMB for both alternatives can be calculated by multiplying the WTP by the QALYs and subtracting the

costs. In that case, a CUA and CBA can be combined. The characteristics, advantages, and disadvantages of the CEAs discussed are summarized in Table 2.

Table 2: Characteristics of the most common types of cost-effectiveness analyses

Type	Outcome	Advantage	Disadvantage
CEA	Natural units of effects	Outcome is likely to be more sensitive than generic outcome	Outcome not comparable with other diseases
CUA	QALYs (utility*duration of life)	Generic outcome comparable with other diseases	Possibly less sensitive than clinical outcome
CBA	Monetary outcome	Allows for comparison	No distinction between costs and consequences/effects

Abbreviations: CBA: cost-benefit analysis, CEA: cost-effectiveness analysis, CUA: cost-utility analysis, QALY: quality-adjusted life year.

Cost-utility analysis (CUA)

As mentioned in Table 2, the comparability of the outcome is one of the advantages of a CUA. When policy makers have to make decisions about the reimbursement of interventions for different diseases, such as governments, it is essential that the outcomes are measured in the same unit in order to make a fair comparison. The QALY is a generic outcome that is used in CUAs (4).

Utilities. A utility is a value anchored with the values 0 (representing death) to 1 (representing full health). Utilities can be derived from individual patients directly or indirectly, but the indirect way is commonly used in cost–effectiveness research. Utility values can be derived indirectly by means of specific questionnaires on HRQOL. Well-known HRQOL instruments such as the EQ-5D (Text box 1.1) consist of questions covering multiple dimensions of functioning (16). The use of HRQOL questionnaires provides insight into to general health and the disabilities of the target population. The reported problems on the EQ-5D questionnaire can be transformed to a utility value using value sets. These value sets are based on the health state valuations of a sample of the general population (17).

QALYs. A QALY, which represents one life-year spent in full health, can be calculated by multiplying a utility value by the remaining life-years. When a patient has a remaining life

expectancy of 10 years that will be spent in a health state with a utility of 0.8, the number of QALYs can be calculated by multiplying 10 by 0.8 which equals 8 QALYs. The combination of HRQOL and life-years makes QALYs suitable for prioritizing interventions in healthcare as their generic character allows for comparison.

Text box 1.1: EQ-5D

The EQ-5D is a comprehensive and widely used generic instrument for measuring HRQOL. The instrument consists of the EQ-5D descriptive system and a visual analogue scale (EQ-VAS) ranging from 0 (worst imaginable health) to 100 (best imaginable health). Five HRQOL dimensions are included in the descriptive system:

- **Mobility**
- **Self-care**
- **Usual activities**
- **Pain/discomfort**
- **Anxiety/depression**

The EQ-5D is available in two forms: the three-level version (EQ-5D-3L) and the five-level version (EQ-5D-5L). The latter version has five answering options instead of three on each of the five dimensions. The levels of the EQ-5D-3L version are 'no problems', 'some problems', and 'severe problems' yielding 243 potential health profiles. A profile of '11111' represents the best possible health state, whereas the profile '33333' represents the worst possible health state. All health states have been valued by representative samples of the general population which allows for deduction of utility scores by means of an additive function. Value sets are available for different populations and countries.

Health-economic modeling

A health-economic model is a mathematical model developed to inform policy decisions regarding the cost-effectiveness of interventions in healthcare (18). In a cost-effectiveness model, available evidence is used to simulate the expected costs and effects of treatment alternatives. However, the methods for modeling the costs and health gains are not always straightforward. Different diseases have specific points to consider when calculating the cost-effectiveness. The following data are required to populate cost-effectiveness models: epidemiological data, cost data, and the effectiveness data of the treatment alternatives under evaluation (18). Using this data as input, the model will generate the relative costs

and effects of the treatment alternatives. An important aspect of health-economic modeling, which is also of interest for this thesis, is to consider the uncertainty surrounding the cost-effectiveness estimates (19). This uncertainty must be quantified in order to identify research priorities and to inform policy decisions (9, 20).

Relevance and addition to current knowledge

In this thesis, HTA methods are applied to interventions for different diseases and health problems that have specific characteristics and methodological challenges. Mental healthcare is one of the areas in healthcare discussed in this thesis, with an emphasis on anxiety disorders. Anxiety disorders are one of the most common mental disorders with an estimated lifetime prevalence of respectively 20% in the Netherlands (21, 22). Specific anxiety disorders highlighted in this thesis are panic disorder and trauma and stressor related anxiety disorders consisting of post-traumatic stress disorder (PTSD) and acute stress disorder. In the Diagnostic and Statistical Manual of Mental Disorders (DSM-V) (23), the last version of the widely used diagnostic manual in psychiatry, trauma and stressor related anxiety disorder are included as a separate category of disorders.

Although multiple pharmacological, psychological, and internet-delivered interventions are proven effective for treating anxiety disorders, little is known about the cost-effectiveness of these interventions. The current evidence base on effectiveness and cost-effectiveness is mainly focused on curative care. More recently, preventive interventions in this field show promising results in terms of cost-effectiveness (24, 25). In this thesis, we investigate and synthesize the available evidence on cost-effectiveness of both preventive and curative interventions for anxiety disorders. We also use methods for quantifying the sources of the uncertainty surrounding the cost-effectiveness estimates in order to identify research priorities.

The second field of interest in this thesis is injury, especially falls among older adults. Falls are the most frequent cause of injury in the Netherlands. They cause more than half of the societal costs resulting from injury (26). Falls are furthermore one of the most frequent causes of death, and the fall-related mortality is still increasing (27). Although effective falls prevention programs exist, the occurrence of falls among older adults is still high. Therefore, there is a need for a broad implementation of effective falls prevention programs. Because the financial resources in healthcare are limited, policy makers should focus on the implementation of falls prevention programs that are not only effective, but also cost-effective. In this thesis, we synthesize available evidence regarding the cost-

effectiveness of these programs in order to facilitate decision making. A comprehensive overview of all published economic evaluations of falls prevention programs and their methodological quality is needed to inform policy decisions, but such an overview has not yet been published.

We furthermore investigate whether the methodology of measuring HRQOL among injury patients can be improved by adding of a cognitive dimension to the EQ-5D-3L, a HRQOL questionnaire that often serves as input for calculating QALYs.

The final area of interest in this thesis is a preventive intervention for subfertile women. In addition to the medical causes of subfertility, modifiable factors such as poor nutrition and lifestyle impair fertility as well (28). Nevertheless, these poor lifestyle behaviors are still common in the reproductive population (29). A preventive coaching program was developed to improve healthy pregnancies in this population (30). In this thesis, we evaluate the cost-effectiveness of this coaching program by means of a cost-effectiveness model. A cost-effectiveness estimate of this preventive intervention can assist decision making regarding potential implementation, reimbursement, and further research.

Aims and outline of this thesis

This thesis explores the utilization of HTA in the field of injury, mental healthcare and prevention with the aim of investigating the cost-effectiveness of interventions and improving the methodology of HRQOL measurement in injury patients. Different scientific approaches have been used, including systematic literature review, health-economic modeling, value of information analysis, and methodological research related to HRQOL measurement. The aims of this thesis are threefold and will be addressed in separate parts of the thesis:

1. To review the cost-effectiveness of preventive interventions in the field of mental healthcare and injury and to assess the methodological quality of the studies **(Part I: Evidence synthesis)**
2. To assess the cost-effectiveness of preventive interventions for panic disorder and subfertility and to identify the main drivers of cost-effectiveness and uncertainty using health-economic modeling techniques **(Part II: Cost-effectiveness modeling)**
3. To investigate the value of alternative approaches for measuring HRQOL in injury patients by means of the EQ-5D-3L **(Part III: Health-related quality of life)**

Part I (*chapter 2, 3,* and *4*) covers the systematic collection and quality appraisal of evidence on prevalence estimates and cost-effectiveness of interventions in healthcare. *Chapter 2* describes a systematic review on the cost-effectiveness of interventions for anxiety disorders. A systematic review on the cost-effectiveness of falls prevention programs for older adults is presented in *chapter 3*. *Chapter 4* describes a systematic review on the prevalence of post-traumatic stress disorder, acute stress disorder and depression following violence-related injury.

In part II (*chapter 5, 6,* and *7*), available evidence on epidemiology, costs, HRQOL, and effectiveness of preventive interventions has been combined in order to model the cost-effectiveness and to identify the main drivers of cost-effectiveness and uncertainty. *Chapter 5* describes a Markov model assessing the cost-effectiveness of an early intervention for subthreshold panic disorder. *Chapter 6* values the uncertainty surrounding this cost-effectiveness estimate by means of Value Of Information (VOI) analysis. Furthermore, the cost-effectiveness of an online coaching program for subfertile women is in presented and discussed in *chapter 7*.

Part III covers methodological aspects of HRQOL measurement by means of the EQ-5D-3L. In *chapter 8*, it is investigated to what extent the addition of a cognitive dimension to the EQ-5D-3L questionnaire has additional value for measuring HRQOL among injury patients.

The results of the studies described in the three parts of this thesis are further discussed in *chapter 9* alongside with their interpretation and implications for research and policy. *Chapter 9* furthermore addresses recommendations for further research.

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PART I

Evidence synthesis

CHAPTER 2

Cost-effectiveness of interventions for treating anxiety disorders: A systematic review

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Abstract

Introduction. Anxiety disorders are highly prevalent mental disorders that constitute a major burden on patients and society. As a consequence, economic evaluations of the interventions have become increasingly important. However, no recent overview of these economic evaluations is currently available and the quality of the published economic evaluations has not yet been assessed. Therefore, the current study has two aims: to provide an overview of the evidence regarding the cost-effectiveness of interventions for anxiety disorders, and to assess the quality of the studies identified.

Methods. A systematic review was conducted using PubMed, PsycINFO, NHS-EED, and the CEA registry. We included full economic evaluations on interventions for all anxiety disorders published before April 2016, with no restrictions on study populations and comparators. Preventive interventions were excluded. Study characteristics and cost-effectiveness data were collected. The quality of the studies was appraised using the Consensus on Health Economic Criteria.

Results. Forty-two out of 826 identified studies met the inclusion criteria. The studies were heterogeneous and the quality was variable. Internet-delivered cognitive behavioral therapy (iCBT) appeared to be cost-effective in comparison with the control conditions. Four out of five studies comparing psychological interventions with pharmacological interventions showed that psychological interventions were more cost-effective than pharmacotherapy.

Limitations. Comparability was limited by heterogeneity in terms of interventions, study design, outcome and study quality.

Conclusions. Forty-two studies reporting cost-effectiveness of interventions for anxiety disorders were identified. iCBT was cost-effective in comparison with the control conditions. Psychological interventions for anxiety disorders might be more cost-effective than pharmacological interventions.

Introduction

Anxiety disorders are highly prevalent mental disorders that constitute a major burden on patients and society (1). With a lifetime prevalence of 19.3% and an annual prevalence of nearly 14% in Europe, they are the most frequent mental disorders (1-3). Not only are anxiety disorders associated with a decreased quality of life, but also with a high economic burden (4). Anxiety disorders are associated with high healthcare utilization in comparison with other mental disorders, especially in general practice (5). Furthermore, the symptoms tend to become chronic when the condition is not properly treated (2). In 2010, the European societal cost for anxiety disorders was estimated at €74.4 billion (6). The Dutch healthcare cost for anxiety disorders was €626 million in 2011, which represents 0.7% of the total healthcare costs in the Netherlands (7).

A systematic review of all published full economic evaluations concerning interventions for treating anxiety disorders and assessing the quality of these evaluations would be helpful for policy makers, who must prioritize interventions. Furthermore, a systematic review will help to identify knowledge gaps. Although systematic reviews and meta-analyses show that psychological interventions, pharmacological interventions (8, 9), and internet-delivered interventions (10) are effective, systematic reviews of cost-effectiveness data on interventions are scarce. Moreover, little is known about the quality of economic evaluations on interventions for anxiety disorders.

Earlier, Konnopka et al. (4) published a systematic review on the cost-effectiveness of interventions for the treatment of anxiety disorders. Konnopka et al. (4) aimed to identify published economic evaluations, but the quality of the included studies was not addressed. Since the review included studies up to 2008, an update was deemed relevant. Therefore, the aim of the current study is two-fold: to provide an overview of the evidence regarding the cost-effectiveness of interventions for anxiety disorders, and to assess the quality of the identified economic evaluations.

Methods

The methods and reporting of this systematic review are in concordance with the PRISMA statement (11). The study protocol is registered in the PROSPERO International Prospective Register of Systematic Reviews (registration number CRD42015026485).

Literature search and study selection

A literature search before April 2016 was conducted in the following databases: PubMed, PsycINFO, the National Health Service Economic Evaluation Database (NHS-EED), and the CEA registry. The NHS-EED is a health-economic database including economic evaluations. The CEA registry includes studies in which a cost-utility analysis was performed. Existing systematic reviews and the references of the studies included were manually searched for relevant studies. We used Medical Subject Headings (MeSH) terms and Psychological Index Terms for searches within the PubMed and PsycINFO databases respectively. In order to identify economic evaluations on anxiety disorders, we selected key terms that were previously used in a recent meta-analysis on the efficacy of interventions for anxiety disorders (8) and combined them with health-economic key terms. An information specialist was involved in the development of the search strategy. A detailed description of the search strategy for every database can be found in appendix 1.1.

Only full economic evaluations were included, meaning that the study compared both costs and effects of two or more conditions (12). Studies were excluded when interventions focused on prevention or relapse prevention, and when studies did not focus primarily on anxiety disorders. The literature search was restricted to articles written in English, German, or French. There were no restrictions on demographic characteristics, patient characteristics, and intervention types. Interventions for all anxiety disorder diagnoses were considered. We included both trial-based economic evaluations (TBEEs) and model-based economic evaluations (MBEEs). In TBEEs costs and effects are measured alongside an effectiveness trial, whereas in MBEEs available evidence is used to simulate long-term consequences on effectiveness and costs.

Interventions were categorized into psychological interventions, pharmacological interventions, and combined interventions. Psychological interventions include non-pharmacological and therapist-led interventions based on cognitive or behavioral therapy. Interventions based on learning theory with elements such as exposure, response prevention and relaxation were considered as behavior therapy (13). An intervention was labelled as cognitive therapy when it involved cognitive restructuring (13). Interventions with combinations of behavior and cognitive therapy were also considered in this category. Internet-delivered interventions were included as a subcategory of the psychological interventions. Because internet-delivered interventions are generally less costly due to minimal therapist contact (10), it is relevant to distinguish these interventions from therapist-led interventions in terms of cost-effectiveness. Internet-delivered interventions

were defined as interventions based on an explicit psychological theory not provided in a clinical setting (14). These interventions provide patients with the same skills and information as therapist-led interventions, but the sessions are entirely or partly provided via Internet and may be supported by therapists via telephone or e-mail.

Pharmacological interventions are medication-based interventions. Interventions were labelled as pharmacological intervention when medication was offered without additional psychological interventions. Combined interventions include both psychological and pharmacological intervention components.

Interventions not meeting the earlier mentioned criteria were not categorized. We categorized interventions in order to draw general conclusions with regard to the cost-effectiveness of different intervention types. Studies in which an incremental cost-effectiveness ratio (ICER) was not reported were not taken into account. We did not specify the intervention categories on target group or diagnosis.

One reviewer (RO) screened the titles and abstracts of the identified studies. In this step, studies that were clearly not eligible based on title and abstract were excluded. Two reviewers (RO and either JL, MH, SH, or SE) independently read the full-text of the remaining studies for eligibility assessment. Disagreements were discussed and resolved during a consensus meeting with a third reviewer.

Data extraction

Two reviewers (RO and either JL, MH, SH, or SE) extracted data on publication year, target population, interventions and comparators, sample size, study design, and effect measurement. We also collected information on synthesis of costs and handling uncertainty; this is described in the appendix.

Quality assessment

The quality of the studies was assessed with the extended Consensus on Health Economic Criteria (CHEC) list (15), which is in concordance with the Cochrane collaboration guidelines (16). The checklist contains 20 items covering internal and external validity aspects of economic evaluation studies. Although the CHEC is not optimal for assessing the quality of MBEEs, we chose the CHEC for the quality assessment of both TBEEs and MBEEs in order to maintain comparability of the results. Each question on the CHEC checklist was scored with either ‘Yes’ (score 1), ‘Suboptimal’ (score 0.5), ‘No’ (score 0), ‘NA’ (not applicable) or ‘Uncertain’ (no score). The ‘Uncertain’ option was used only when information on an item was not entirely clear. We did not contact authors when the

published information was insufficient to assign a score.

Prior to the final quality assessment, three included studies were randomly chosen for test reviewing and were independently assessed by all reviewers. The scoring instruction was refined after discussing the results. A detailed description of the scoring instruction can be found in appendix 1.2. Each study was assessed independently by two reviewers (RO and either JL, MH, SH or SE). Disagreements were resolved through a consensus meeting between the two reviewers. A third reviewer was involved when consensus was not reached.

Outcomes

The ICERs of the reference-case analysis were reported as the outcome for all included studies. For example, ICERs are expressed as costs per quality-adjusted life year (QALY) gained or costs per any (clinical) outcome. In case an ICER was not reported, we described the health-economic results narratively. In order to compare price levels between countries, all ICERs were converted to US$ by using Purchasing Power Parity (PPP) rates (17). Thereafter, all ICERs were expressed as 2014 US$ by using the Consumer Price Index (18). Consequently, differences due to purchasing power and inflation were eliminated, allowing comparison of the cost data. In order to maintain comparability of the results of the included cost-utility analyses (CUAs) with QALY as outcome, we applied an overall willingness-to-pay (WTP) threshold of US$ 50,000 per QALY, which is commonly used in the USA (19). The WTP threshold refers to the maximum amount a country or society is willing to pay for a particular health gain (19). When an ICER exceeds the WTP threshold, the intervention studies can be regarded as not cost-effective in comparison with the control condition.

Results

Literature search and study selection

In total, the search strategy yielded 826 articles. After excluding 67 duplicates, the titles and abstracts of 759 articles were screened for relevance. Three studies were found by additional reference searching. Title and abstract screening resulted in the exclusion of 707 articles, mainly because they were not (full) economic evaluations or not primarily focused on anxiety disorders. Fifty-two articles were left for full-text eligibility assessment, of which 11 were excluded for several reasons: not full-economic evaluations (n=6), focused on relapse prevention (n=1), not primarily focused on anxiety disorders (n=3), or

non-original research (n=1). Finally, 42 articles were included for analysis. All studies included in the review by Konnopka et al. (4) (n=11) were identified and also included in the current review. A flow chart of the study identification process is presented in Figure 1.

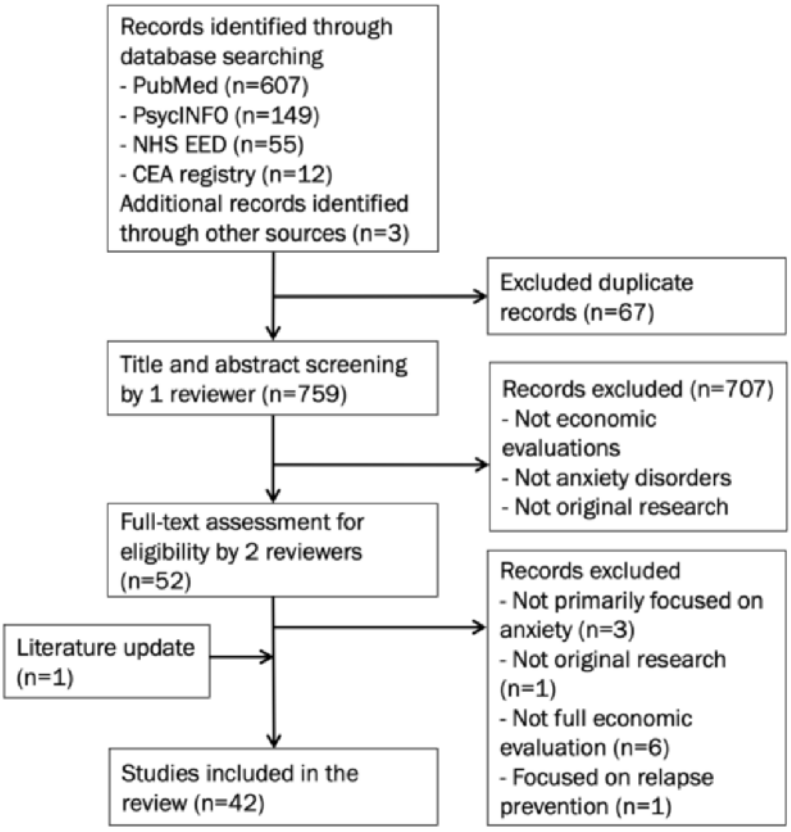

Figure 1: Flow chart of the study identification process

Data extraction

Overview of the included studies. The main characteristics of the studies included are presented in Table 1. The most recent studies were published in 2015 (20-25), and the least recent studies were published in 2000 (26, 27). Most studies were conducted in Western countries, of which half are in Europe: UK (n=6), Sweden (n=6), the Netherlands (n=3), Spain (n=3), Germany (n=2), and Portugal (n=1). The remaining studies were conducted in the USA (n=10), Australia (n=6), Canada (n=4), and China (n=1).

The majority (n=30) of the studies were TBEEs (71.4%), whereas twelve studies (28.6%)

were based on economic modelling. Two studies used both TBEE and MBEE components, but were regarded as TBEEs in the current review (28, 29). In accordance with the Consolidated Health Economic Evaluation Reporting Standards (CHEERS), we distinguished healthcare and societal economic perspectives (30). A societal perspective was adopted by 13 studies and a healthcare perspective was adopted by 19 studies. Ten studies did not explicitly report the study perspective. In six studies, the time horizon was shorter than six months (20, 31-35). Twenty-eight studies used a time horizon of between 6 months and 18 months. Four studies used a time horizon of two years (21, 25, 36, 37). The remaining studies had time horizons of four years (38), five years (24) and 31 years (39). In one study, the time horizons for the costs (two months) and effects (one year) differed (22). Eight studies reported funding by the pharmaceutical industry.

Data on study population and treatment alternatives are presented in Table 2. More than half of the studies included patients with one specific anxiety disorder: panic disorder (PD) (n=11) (26, 27, 33, 36, 37, 40-45), generalized anxiety disorder (GAD) (n=9) (28, 29, 31, 35, 46-50), social anxiety disorder (SAD) (n=5) (23, 24, 38, 51, 52), post-traumatic stress disorder (PTSD) (n=4) (25, 39, 53, 54), and obsessive-compulsive disorder (OCD) (n=3) (20, 21, 34). Two studies included patients with PD or GAD (55, 56), and two studies included patients with PD, SAD, GAD or PTSD (57, 58). One study included patients with PD or phobia (32). Furthermore, four studies focused on patients with any anxiety disorder (3, 22, 59, 60). Kolbasovsky et al. (61) only included patients who visited a hospital emergency department due to panic.

The majority of the studies (n=38) targeted adult patients, although four studies focused on other age categories. Bodden et al. (59) included children aged 8–18 years, Gospodarevskaya and Segal (39) included sexually abused children in a hypothetical cohort with a baseline age of 10 years, and Dear et al. (22) included patients aged 60 years and older. One study included both adults and children younger than 16 years (25).

Effects, costs, and uncertainty. Information on effect measurement and valuation is described in Table 2. Ten studies included both a CUA and a cost-effectiveness analysis (CEA). In CUAs outcomes were expressed as costs per QALY (n=18), disability-adjusted life years (DALYs) (n=3), or years lost due to disability (YLDs) (n=1). In studies with CEAs outcomes were expressed as costs per clinical endpoints or natural units, for example anxiety-free days. Eighteen studies included only a CEA and 13 only a CUA. In the majority of the CUAs with QALYs as outcome (77.3%), utilities were elicited with the EuroQol 5D (EQ-5D). The remaining studies used the Assessment of Quality of Life (AQoL) or Short

Form (SF). For one study, the utility measurement was unclear (41). A cost-benefit analysis (CBA), in which costs and effects are both expressed in monetary terms, was conducted in one study (58).

Detailed information on cost identification, cost measurement, valuation, and handling uncertainty are presented in the appendix (1.5-1.6). Twelve out of 30 TBEE studies included healthcare costs and patient and family costs including productivity losses. Five studies only included direct treatment costs, i.e. costs that are directly related to the intervention being studied. The remaining TBEEs either included healthcare costs or healthcare and patient and family costs. The majority of the TBEEs (70%) described the costs measurement method; for the remaining studies (30%) it was unclear how costs were measured. In seven TBEEs (23.3%) it was not clearly reported how the measured costs were valued. In 20 TBEEs sample uncertainty was handled by means of bootstrapping. In the remaining ten studies, a bootstrapping procedure was not performed. Additional sensitivity analyses were performed in 53.3% of the TBEEs.

Six out of 12 MBEEs only included healthcare costs; three included only direct healthcare costs, two included direct treatment costs and productivity losses, and one study included healthcare costs and patient and family costs. The cost sources were reported in all MBEEs. Both probabilistic and deterministic sensitivity analyses were conducted in ten MBEES, whereas in three MBEEs either a probabilistic or a deterministic sensitivity analysis was conducted.

Table 1: Main characteristics of economic evaluations of interventions for anxiety disorders

ID	Authors (year)	Country	Economic evaluation	Study type	Analysis	Perspective	Time horizon	Industry funding
1	Andersson et al. (20)	Sweden	TBEE	RCT	CEA, CUA	Societal	4 months	No
2	Andersson et al. (21)	Sweden	TBEE	RCT	CEA	Societal	2 years	No
3	Bergstrom et al. (40)	Sweden	TBEE	RCT	CEA	NR	6 months	No
4	Bodden et al. (59)	The Netherlands	TBEE	RCT	CEA, CUA	Societal	15 months	No
5	De Salas-Cansado et al. (28)	Spain	Combined [1]	Combined [1]	CUA	Healthcare	6 months	Pfizer
6	De Salas-Cansado et al. (29)	Spain	Combined [1]	Combined [1]	CUA	Healthcare	6 months	Pfizer
7	Dear et al. (22)	Australia	TBEE	RCT	CUA	Healthcare	1 year (effects), 2 months (costs)	No
8	Egger et al. (23)	Germany	TBEE	RCT	CEA, CUA [2]	Societal	6 months	No
9	Goorden et al. (55)	The Netherlands	TBEE	RCT	CUA	Societal	1 year	No
10	Gospodarevskaya et	Australia	MBEE	Decision tree model +	CUA	Healthcare	31 years	No

	al. (39)			Markov model				
11	Guest et al. (46)	UK	MBEE	Decision tree model	CEA	Healthcare	6 months	Wyeth
12	Hedman et al. (51)	Sweden	TBEE	RCT	CEA, CUA	Societal	6 months	No
13	Hedman et al. (38)	Sweden	TBEE	RCT	CEA, CUA	Societal	4 years	No
14	Heuzenroeder et al. (56)	Australia	MBEE	Epidemiologically-based CUA	CUA	Healthcare	1 year	No
15	Iskedjian et al. (31)	Canada	MBEE	Decision tree model	CEA	Societal	24 weeks	Lundbeck
16	Issakidis et al. (57)	Australia	MBEE	Epidemiologically-based CUA	CUA	Healthcare	1 year	No
17	Joesch et al. (58)	USA	TBEE	RCT	CBA	Healthcare	18 months	Unclear
18	Jorgensen et al. (47)	UK	MBEE	Decision tree model	CEA	Societal	9 months	Lundbeck
19	Katon et al. (41)	USA	TBEE	RCT	CEA, CUA	Healthcare	1 year	No
20	Katon et al. (42)	USA	TBEE	RCT	CEA	Healthcare	1 year	Unclear
21	Kolbasovsky et al. (61)	USA	TBEE	RCT	CEA	NR	6 months	No
22	Konig et al. (60)	Germany	TBEE	RCT (cluster)	CUA	Societal	9 months	No
23	Lambert et al. (43)	UK	TBEE	RCT	CEA, CUA	Healthcare (GP)	10 months	No
24	Le et al. (53)	USA	TBEE	RCT and preference	CUA	Societal	1 year	Pfizer

				trial [3]				
25	Marchand et al. (36)	Canada	TBEE	RCT	CEA	Healthcare	2 years	No
26	Mavissakalian et al. (26)	USA	MBEE	Markov model	CUA	Healthcare	18 months	No
27	Mavranezouli et al. (48)	UK	MBEE	Decision tree model	CUA	Healthcare	42 weeks	No
28	Mavranezouli et al. (24)	UK	MBEE	Decision tree model + Markov model	CUA	Healthcare	5 years and 12 weeks	No
29	McCrone et al. (32)	UK	TBEE	RCT	CEA	Healthcare	1 month	No
30	McHugh et al. (44)	USA	TBEE	RCT	CEA	NR	15 months	No
31	Mihalopoulos et al. (25)	Australia	MBEE	Decision tree model	CUA	Healthcare	5 years	No
32	Nordgren et al. (3)	Sweden	TBEE	RCT	CEA, CUA	NR	1 year	No
33	Otto et al. (27)	USA	TBEE	Unclear	CEA	NR	1 year	No
34	Poirier-Bisson et al. (45)	Canada	TBEE	Cohort [4]	CEA	NR	6 months	No
35	Roberge et al. (33)	Canada	TBEE	RCT	CEA	Societal	3 months	No
36	Schnurr et al. (54)	USA	TBEE	RCT	CEA	NR	6 months	No
37	Silva Miguel et al. (49)	Portugal	MBEE	Patient-level simulation	CEA, CUA	Healthcare	1 year	Pfizer
38	Titov et al. (52)	Australia	TBEE	RCT [5]	CEA	NR	6 months	No

39	Tolin et al. (34)	USA	TBEE	RCT	CEA	NR	3 months	No
40	Van Apeldoorn et al. (37)	The Netherlands	TBEE	RCT	CEA	Societal	2 years	No
41	Vera-Llonch et al. (50)	Spain	MBEE	Patient-level simulation	CEA, CUA	Healthcare	1 year	Pfizer
42	Zhang et al. (35)	China	TBEE	Trial [6]	CEA	NR	3 months	No

Abbreviations: CEA: cost-effectiveness analysis; CUA: cost-utility analysis; MBEE: model-based economic evaluation; NR: not reported; RCT: randomized controlled trial; TBEE: trial-based economic evaluation.

[1] Both MBEE and TBEE components.

[2] CUA included in sensitivity analysis, not in the reference-case.

[3] Hybrid design: patients were allocated to treatment choice/no choice and subsequently to exposure/pharmacotherapy.

[4] Cohort design with prior to the study a randomization of the sequence of treatment conditions.

[5] Two RCTs combined.

[6] Randomization not mentioned.

Table 2: Characteristics of and results for economic evaluations of interventions for anxiety disorders

ID	Target population	Treatment alternatives (n) [1]	Effect measurement and valuation [2]	Discount rates	Valuation year	Results and ICERs (2014 US$)
1	Patients with OCD	I: iCBT (50); II: Internet-based supportive therapy	Y-BOCS, QALYs (EQ-5D)	NA	2013	ICER iCBT versus internet-based supportive therapy: $947/relapse avoided; $7,307/QALY gained. iCBT resulted in greater effects and more QALYs at higher cost.
2	Patients with OCD	I: Additional booster treatment after iCBT (47), II: No additional booster treatment after iCBT (46)	Y-BOCS	NR	Unclear	ICER additional booster treatment versus no booster treatment after receiving iCBT: $1,489/relapse avoided. The additional booster treatment was more effective at higher cost.
3	Patients with PD, with or without agoraphobia	I: iCBT (53); II: Group CBT (60)	PDSS, CGI	NA	Unclear	iCBT has superior cost-effectiveness ratios in comparison with group CBT. ICER NR.
4	Children (aged 8-18 years) with anxiety disorder	I: Family CBT (57); II: Individual CBT (59)	ADIS-IV, QALYs (EQ-5D)	Cost 4%, QALY unclear	2003	Individual CBT is dominant for both CEA and CUA. Individual CBT is more effective and less costly in comparison with family CBT. ICER NR.
5	Patients with refractory GAD	I: Pregabalin (451); II: Usual care (451)	QALYs (EQ-5D)	NA	Unclear	ICER pregabalin versus usual care: $22,590/QALY gained. Pregabalin treatment resulted in more QALYs at higher costs.
6	Benzodiazepine-	I: Pregabalin (157); II:	QALYs (EQ-5D)	NA	2008	ICER pregabalin versus SSRI/SNRI:

	refractory patients with GAD	SSRI/SNRI (125)				$38,670/QALY gained. Pregabalin treatment resulted in more QALYs at higher costs.
7	Elderly aged 60 years and older who experience symptoms of anxiety, stress and worry	I: iCBT (35); II: Waiting list (37)	QALYs (EQ-5D)	NA	2013	ICER iCBT versus waiting list: $6,175/QALY gained. iCBT treatment resulted in more QALYs at higher cost.
8	Adults (aged 18-70 years) with SAD	I: CBT (209); II: Psychodynamic therapy (207); III: Waiting list (79)	LSAS-SR, QALYs (EQ-5D)	NA	2008	ICERs CBT versus waiting list: $4,899/response, $7,843/remission. ICERs psychodynamic therapy versus waiting list: $6,718/response, $14,544/remission. Both interventions resulted in greater effects at higher cost.
9	Patients with PD or GAD	I: Collaborative Stepped Care (114); II: Usual care (66)	QALYs (EQ-5D)	NA	Unclear	ICER Collaborative Stepped Care versus usual care: -$6,289/QALY gained. Collaborative Stepped Care dominated usual care.
10	Sexually abused children with PTSD	I: Trauma-focused CBT; II: Trauma-focused CBT+SSRI; III: Non-directive counselling; IV: no treatment	QALYs (AQoL-4D)	5% (cost and QALY)	2010/2011	Non-directive counselling is dominated by all active treatments. ICER Trauma-focused CBT+SSRI versus Trauma-focused CBT alone: $2,097/QALY gained. Trauma-focused CBT+SSRI resulted in more QALYs at higher costs in comparison with trauma-focused CBT only.
11	Non-depressed patients with GAD	I: Venlafaxine XL; II: Diazepam	CGI	NA	2000/2001	ICERs venlafaxine XL versus diazepam: $821/additional %

						remission at 6 months; $638/additional % relapse avoided. Venlafaxine XL resulted in greater effects at higher costs.
12	Patients with SAD	I: iCBT (64); II: Group CBT (62)	LSAS-SR, QALYs (EQ-5D)	NA	Unclear	CEA; ICER iCBT versus group CBT: -$7,652/point improvement on LSAS-SR. iCBT dominates group CBT. CUA; ICER iCBT versus group CBT: -$19,356/QALY gained. iCBT dominated group CBT.
13	Patients with SAD	I: iCBT (64); II: Group CBT (62)	LSAS-SR, QALYs (EQ-5D)	NR	Unclear	CUA; ICER iCBT versus group CBT: -$7,469/QALY gained. iCBT dominates group CBT. CEA; ICER iCBT versus group CBT: $10,270/point improvement on LSAS-SR. iCBT was less effective at lower costs in comparison with group CBT.
14	Patients (aged 18 years and older) with GAD or PD	*GAD*; I: CBT, II: SNRI, III: Usual care. *PD*; I: CBT, II: Paroxetine, III: Imipramine, IV: Usual care	DALYs	NA	2000	*GAD*; ICER CBT versus usual care: $7,252/DALY saved. *PD*; ICER CBT versus usual care: $7,147/DALY saved. CBT was the most cost-effective intervention for both GAD and PD.
15	Patients with GAD	I: Escitalopram; II: Paroxetine	CGI	NA	2005	*Canadian healthcare perspective;* ICER escitalopram versus paroxetine: $2,358/symptom-free year. Escitalopram resulted in more effects at higher costs. *Societal perspective;* escitalopram is

						dominant over paroxetine.
16	Patients with PD, SAD, GAD, or PTSD	I: Evidence-based optimal treatment; II: Current treatment	DALYs	NA	1997/1998	Optimal care yields greater health gains at similar costs. ICERs NR.
17	Adults (aged 18-75 years) with PD, GAD, SAD, or PTSD	I: CALM (349); II: Usual care (341)	QALYs (EQ-5D, SF-12)	NR	2009	The mean incremental net benefit of CALM versus usual care is positive when an anxiety free day is valued at $3 or more. The mean incremental net benefit is positive when a QALY is worth $3,829 or more.
18	Patients with moderate to severe GAD	I: Escitalopram; II: Paroxetine	CGI	NA	2005	Escitalopram yielded greater effectiveness at lower costs in comparison with paroxetine. ICER NR.
19	Patients (aged 18-70 years) with PD	I: CBT+SSRI (119); II: Usual care (113)	ASI, QALYs [3]	NA	Unclear	ICERs CBT+SSRI versus usual care: $10/additional anxiety free day, and costs per QALY gained ranging from $17,160 to $30,030. CBT+SSRI is associated with greater effects at higher costs in comparison with usual care.
20	Patients aged 18-65 with PD	I: Collaborative care (57); II: Usual care (58)	ASI	NA	Unclear	ICER Collaborative care versus usual care: -$4/anxiety free day. Collaborative care dominated Usual care.
21	Patients (aged 18 years and older) discharged from emergency department with a	I: Intervention care (307); II: Usual care (300)	Emergency department visits	NA	Unclear	In the 6 months following emergency department discharge, intervention care resulted in lower emergency department visits at lower facility costs in comparison with usual care.

	visit related to anxiety					Psychiatric outpatient costs were equal between conditions. ICER NR.
22	Patients (aged 18-65 years) with anxiety disorder	I: Optimised care (201); II: Usual care (188)	QALYs (EQ-5D)	NA	2006	Optimized care was dominated by usual care. Optimized care resulted in less QALYs at higher costs. ICER NR.
23	Patients (aged 18-65 years) with PD	I: Occupational therapy-led lifestyle intervention (57); II: Routine GP care (60)	BAI, QALYs (EQ-5D)	NA	2001/2002	ICERs occupational therapy-led lifestyle intervention versus routine GP care: $83/unit of BAI improvement; $17,696/QALY gained. Occupational therapy-led lifestyle intervention yielded more effects at higher cost.
24	Patients (aged 18-65 years) with PTSD	I: Prolonged exposure (109); II: Sertraline (91) (either by choice or randomized)	QALYs (EQ-5D)	NA	2012	*Overall treatment effect*; prolonged exposure was dominant to sertraline. *Treatment choice*; being able to choose between treatments was dominant over treatment assignment. ICER preferring and receiving prolonged exposure versus preferring pharmacotherapy but receiving prolonged exposure: $29,930/QALY gained. ICER preferring and receiving pharmacotherapy versus preferring prolonged exposure but receiving pharmacotherapy: $27,273/QALY gained.
25	Patients with PD	I: CBT and pharmacotherapy, II: CBT	GFI	NR	Unclear	CBT was more effective at lower costs in comparison with CBT and pharmacotherapy combined. ICER NR.

26	Patients with PD	I: Imipramine without maintenance, II: Imipramine with half-dose maintenance, III: Imipramine with full-dose maintenance	QALYs (NR)	NR	1997	The total costs and effects of imipramine with half-dose maintenance and imipramine with full-dose maintenance were similar and both cost saving in comparison with imipramine without maintenance. ICER NR.
27	Patients with GAD	6 pharmacological treatments and placebo	QALYs (SF-36)	NA	2011	Sertraline resulted in the highest QALY gain at the lowest cost. ICERs NR.
28	Patients with SAD	Multiple pharmacological treatments, psychological treatments, placebo, waiting list	QALYs (EQ-5D)	3.5% (cost and QALY)	2015	CBT according the Clark & Wells model was the most cost-effective treatment option, followed by individual CBT and phenelzine.
29	Patients with PD and phobia	I: Computer-guided self-exposure (NR); II: Clinician guided self-exposure (NR); III: Computer-guided relaxation	SRMP	NA	Unclear	ICER computer-guided self-exposure versus computer-guided relaxation: $108/extra unit of improvement on the SRMP. ICER clinician-guided self-exposure versus computer-guided relaxation: $169/extra unit of improvement on the SRMP.
30	Patients with PD	I: CBT+imipramine (65); II: CBT+placebo (63); III: CBT (77); Imipramine (83); IV: Placebo (24)	PDSS	NA	2006	Individual treatment resulted in greater cost-efficiency in comparison with combined treatment. Imipramine was most cost-efficient in the acute phase (3 months). CBT was the most cost-efficient treatment in the

						maintenance phase (6 months). ICERs NR.
31	Adults and children under 16 years with PTSD	I: Trauma-focused CBT (adults and children); II: SSRI (adults only); III: Usual care	QALYs (AQoL-4D), DALYs	3% (cost and QALYs)	2012	*Adults;* ICER Trauma-focused CBT versus usual care: $10,715/DALY and $12,724/QALY gained. ICER SSRI versus usual care: $154/QALY gained. *Children <16 years;* ICER Trauma-focused CBT versus usual care: $5,358/DALY and $5,960/QALY gained. Trauma-focused CBT (adults and children) and SSRI (adults) resulted in more QALY/DALYs at higher cost in comparison with usual care.
32	Adults (aged 18 years and older) with anxiety disorder	I: iCBT (50); II: Attention control group [4] (50)	CORE-OM, QALYs (EQ-5D)	NA	Unclear	ICERs iCBT versus attention control group: -$1,855/incremental improvement on CORE-OM; -$7,650/QALY gained. iCBT dominates attention control.
33	Patients with PD	I: Pharmacotherapy (40); II: CBT (20); III: Group CBT (20)	CGI	NA	Unclear	Treatment effects were equal for all groups: pharmacotherapy resulted in the highest costs and CBT was associated with the lowest costs. ICERs NR.
34	Patients with PD with a chief complaint of non-cardiac chest pain	I. Panic management (24); II. SSRI (11); III. Brief CBT (19); IV. Usual care (15)	ADIS-IV	NA	Unclear	ICER panic management versus usual care: $103/point of improvement on ADIS-IV. ICER SSRI versus usual care: $177/point of improvement on ADIS-IV. ICER brief CBT versus usual care:

						$256/point of improvement on ADIS-IV. All interventions were more effective at higher cost in comparison with usual care.
35	Adults (aged 18-65 years) with PD with agoraphobia	I: CBT (33); II: Brief CBT (32); III: Group CBT (35)	GFI, effect sizes [5]	NA	2000	In comparison with CBT, brief CBT and group CBT were less costly and had superior cost-effectiveness ratios. ICERs NR.
36	USA veterans with PTSD	I: Collaborative care (96); II: Usual care (99)	PDS	NA	2010	The effects and total costs were equal for both interventions. ICER NR.
37	Patients with moderate to severe GAD	I: Pregabalin; II: Venlafaxine XR	HAM-A, QALYs (EQ-5D)	NA	Unclear	ICER pregabalin versus venlafaxine XR: $138/additional week with no or minimal anxiety; $47,545/QALY gained. Pregabalin resulted in more effects at higher cost in comparison with venlafaxine XR.
38	Patients (aged 18 years and older) with SAD	I: Shyness program (93); II: Waiting list (100)	SIAS and SPS, conversed to YLD	NA	2008	ICER NR. [6]
39	Patients (aged 18 years and older) with OCD (moderate severity, having symptoms for at least 1 year)	I: Stepped care ERP (18); II: ERP (12)	Y-BOCS	NA	Unclear	Stepped care ERP was equally as efficacious as ERP, but stepped care ERP was associated with significantly lower cost in comparison with ERP. ICER NR.
40	Patients (aged 18-65) with PD with or without agoraphobia	I: CBT (52); II: SSRI (47); III: CBT+SSRI (49)	HAM-A	NR	2005	ICERs NR. CBT dominates SSRI, and CBT+SSRI was more effective at higher cost in comparison with SSRI alone.

41	Patients with moderate to severe GAD	I: Pregabalin; II: Venlafaxine XR	HAM-A, QALYs (EQ-5D)	NA	2007	ICER Pregabalin versus venlafaxine XR: $42/additional week with no or minimal anxiety, $3,617/QALY gained. Pregabalin resulted in more effects at higher cost in comparison with venlafaxine XR.
42	Participants (aged 18-65) with GAD	I: Venlafaxine (50); II: Citalopram (50)	HAM-A	NA	Unclear	ICER of $4/% cured. Venlafaxine treatment resulted in more effects at higher cost in comparison with citalopram.

Abbreviations: ADIS-IV: Anxiety Disorders Interview Schedule; AQoL-4D: Assessment of Quality of Life; ASI: Anxiety Sensitivity Index; BAI: Beck Anxiety Inventory; CBT: cognitive behavioral therapy; CGI: Clinical Global Impressions; CORE-OM: Clinical Outcomes in Routine Evaluation Outcome Measure; DALY: disability-adjusted life year; ERP: exposure and response prevention; EQ-5D: EuroQol 5D; GAD: generalized anxiety disorder; GFI: Global Functioning Index; HAM-A: Hamilton Anxiety Rating Scale; iCBT: internet delivered CBT; ICER: incremental cost-effectiveness ratio; LSAS-SR: Liebowitz Social Anxiety Scale; NA: not applicable; NR: not reported; OCD: obsessive-compulsive disorder; PD: panic disorder; PDS: Posttraumatic Diagnostic Scale; PDSS: Panic Disorder Severity Scale; PTSD: post-traumatic stress disorder; QALY: quality-adjusted life year; SAD: social anxiety disorder; SF-36/12: Short Form 36/12; SIAS: Social Interaction Anxiety Scale; SNRI: Serotonin–norepinephrine reuptake inhibitor; SRMP: self-rated main problem; SPS: Social Phobia Scale; SSRI: selective serotonin reuptake inhibitor; Y-BOCS: Yale–Brown Obsessive Compulsive Scale; YLD: years lived with disability.

[1] Sample size (n) of the intervention conditions applicable only to trial-based economic evaluations.

[2] Valuation method of utilities applicable only to cost-utility analyses.

[3] Valuation method unclear.

[4] Attention control group received treatment after 10 weeks.

[5] Effect sizes of multiple outcome measures used.

[6] Results unclear; the cost-effectiveness of the Shyness program versus waiting list is not described in the results.

Quality assessment. Table 3 describes the CHEC quality scores. The total score is expressed as the percentage of the maximum score for each individual study. The quality of the studies was variable. The average total score was 73%, with a range of 38–94%. None of the studies included met all the CHEC criteria. On average, the items on generalizability of the results and ethical distribution had the lowest scores. Twelve studies discussed the generalizability of the study results properly, whereas in the remaining studies (n=30) the generalizability of the study results was poorly or not described. Three out of 42 studies discussed ethical and distributional issues. On average, the items on appropriateness of the economic study designs and outcome measurement had the highest scores. The economic study designs and outcome measurement were considered appropriate for all studies.

Outcomes. The health-economic results in terms of ICERs of the reference-cases are presented in Table 2. ICERs were reported in 19 studies that included a CUA with QALYs as outcome. In six of these studies, the interventions studied were dominant over the control condition, meaning that the interventions in these studies resulted on average in more QALYs at lower costs in comparison with the control conditions (3, 38, 51, 55, 59, 60). In the remaining 13 CUAs with QALYs as outcome, the studied interventions resulted in more QALYs at higher costs in comparison with the control condition (20, 22, 23, 25, 28, 29, 39, 41, 43, 46, 49, 50, 53). However, the ICERs of all these studies were below the WTP threshold of $50,000 per QALY gained. Two studies in which a CEA was conducted had a dominant ICER (31, 41).

Psychological interventions. Two studies compared a psychological intervention with another psychological intervention or inactive treatment (23, 59), and five studies compared psychological interventions with pharmacological interventions or multiple interventions (24, 25, 45, 53, 56). In four out of these five studies, psychological interventions were more cost-effective in comparison with the control condition or conditions. When comparing psychological interventions with other psychological interventions, individual CBT appeared to be cost-effective in comparison with family CBT for children aged 8–18 years (59), and CBT and psychodynamic therapy appeared to be cost-effective in comparison with a waitlist condition (23). iCBT was identified as the only internet-delivered intervention. iCBT was cost-effective in comparison with all control conditions consisting of group CBT and inactive treatment (3, 20, 22, 38, 51).

Table 3: CHEC quality assessment

Item	Study ID																
	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17
1. Is the study population clearly described?	1	1	1	1	1	1	1	1	0	1	1	1	1	1	0.5	1	1
2. Are competing alternatives clearly described?	0.5	1	1	0.5	0.5	0.5	1	0.5	0.5	1	0.5	1	1	1	0.5	0.5	1
3. Is a well-defined research question posed in answerable form?	0.5	0.5	1	1	1	1	1	1	1	1	1	1	1	1	1	1	0
4. Is the economic study design appropriate to the stated objective?	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
5. Are the structural assumptions and the validation methods of the model properly reported (models only)?	NA	NA	NA	NA	NA	NA	NA	NA	NA	1	1	NA	NA	1	1	1	NA
6. Is the chosen time horizon appropriate in order to include relevant costs and consequences?	0	1	1	1	1	1	0	0.5	1	1	1	0.5	1	1	0	1	1
7.Is the actual perspective chosen appropriate?	1	1	0	1	0.5	0.5	0.5	1	1	0.5	0.5	1	1	0.5	1	0.5	0
8. Are all important and relevant costs for each alternative identified?	1	1	0	1	1	1	1	1	1	0	0	1	1	0	0.5	1	1
9 .Are all costs measured appropriately in physical units?	1	1	0	1	1	1	1	1	1	1	1	1	1	1	1	1	1
10. Are costs valued appropriately?	0.5	0.5	0	1	1	1	1	1	0.5	1	1	0	0	1	1	1	1
11. Are all important and relevant outcomes for each alternative identified?	1	0.5	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
12. Are all outcomes measured appropriately?	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
13. Are outcomes valued appropriately?	1	NA	NA	1	0.5	1	1	1	1	1	NA	1	1	1	NA	1	1
14. Is an appropriate incremental analysis of costs and outcomes of alternatives performed?	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	0
15. Are all future costs and outcomes discounted appropriately?	NA	0	NA	0.5	NA	NA	NA	NA	NA	1	NA	NA	0	NA	NA	NA	0
16. Are all important variables, whose values are uncertain, appropriately subjected to sensitivity analysis?	0.5	0.5	0.5	1	1	1	0.5	1	0.5	1	1	1	1	1	1	1	0.5
17. Do the conclusions follow from the data reported?	0.5	1	1	1	1	1	1	1	1	0	0.5	1	1	1	0	1	1
18. Does the study discuss the generalizability of the results to other settings and patient/client groups?	1	0.5	0	0	1	1	0.5	0.5	0	1	0.5	0.5	0	1	0	0.5	0
19. Does the article/ report indicate that there is no potential conflict of interest of study researcher(s) and funder(s)?	0	1	1	0.5	1	1	0.5	1	1	0.5	0.5	1	1	0	0.5	0	1
20.Are ethical and distributional issues discussed appropriately?	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0	0	0
Score [1]	69	75	62	82	86	89	78	86	75	80	75	83	79		67	82	66

Table 3 (continued): CHEC quality assessment

	Study ID																							
Item	18	19	20	21	22	23	24	25	26	27	28	29	30	31	32	33	34	35	36	37	38	39	40	41	42
1	0.5	1	1	1	0.5	1	1	1	0.5	0.5	0.5	1	0.5	1	1	0.5	1	1	1	0.5	1	1	1	0.5	1
2	0.5	1	1	1	1	1	1	0.5	0.5	0.5	1	0.5	0.5	1	1	0.5	1	0.5	0.5	0.5	1	1	0.5	0.5	1
3	1	1	1	1	1	1	0.5	1	1	1	1	0.5	1	1	0.5	1	1	1	1	1	1	1	1	1	0.5
4	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
5	1	NA	NA	NA	NA	NA	NA	NA	1	0.5	1	NA	NA	1	NA	NA	NA	NA	NA	1	NA	NA	NA	1	NA
6	0.5	1	1	1	0.5	1	1	1	1	1	0.5	0	1	1	1	1	0.5	0	0.5	1	0	0.5	1	1	0
7	1	0.5	0.5	0	1	0.5	1	0.5	0.5	0.5	1	0	0	0.5	0	0	0	1	0	0.5	0	0.5	1	0.5	0
8	0.5	1	1	X	1	1	1	0.5	1	1	1	0	0.5	0	1	0	1	0.5	0.5	1	0	1	1	1	1
9	1	1	1	0	1	1	1	1	1	1	1	X	0.5	1	1	0.5	1	1	0.5	1	0	0.5	1	1	1
10	1	1	0.5	0	1	1	1	1	0.5	1	1	0.5	1	1	0	0.5	0.5	1	1	0.5	0.5	1	1	1	0
11	1	1	1	0	1	1	1	0.5	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
12	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
13	NA	1	NA	NA	1	1	1	NA	0	1	1	NA	NA	1	1	NA	NA	NA	NA	1	NA	NA	NA	1	NA
14	0.5	1	1	0	1	1	1	0.5	0.5	1	1	1	0	1	1	0	1	1	0	1	0	0	0.5	1	0.5
15	NA	NA	NA	NA	NA	NA	NA	0	0	NA	1	NA	0	1	NA	NA	NA	NA	NA	NA	NA	NA	0	NA	NA
16	1	1	1	0	1	1	1	0	0.5	1	1	1	0	1	1	0	0.5	0	0	1	0	0	1	1	0
17	0	1	1	1	1	1	1	1	0.5	1	1	1	0	1	1	0.5	1	1	0.5	0.5	0	1	1	0.5	0
18	0	1	0	1	1	0	1	0	0	0.5	0.5	0	0.5	1	0	0	0	0	1	0	0	1	0	0	0
19	0.5	1	0.5	0	1	1	1	0	0	1	1	0.5	1	1	0.5	0	1	0	1	1	0	1	1	1	0
20	0	0	0	1	0	0	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0
Score [1]	67	92	79	53	89	86	92	58	58	82	88	53	53	93	72	44	74	65	62	76	38	74	78	79	47

0: no; 0.5: suboptimal; 1: yes; X: uncertain; NA: not applicable.

[1] Score expressed as percentage of the maximum score, items scored with NA were excluded.

Pharmacological interventions. In seven studies, a pharmacological intervention was compared with another pharmacological intervention or usual care (28, 29, 31, 35, 46, 49, 50). All these studies included patients with GAD, and therefore their results are not applicable to other anxiety disorders. Pregabalin appeared to be cost-effective in comparison with usual care, SSRIs and venlafaxine (28, 29, 49, 50). It should be noted that pharmaceutical companies financially supported all studies involving pregabalin. Furthermore, venlafaxine appeared to be cost-effective in comparison with diazepam and citalopram (35, 46), and escitalopram was more cost-effective than paroxetine (31). As mentioned before, five studies compared psychological interventions with pharmacological interventions or multiple interventions. In one of these studies, SSRIs were cost-effective in comparison with usual care and more cost-effective than a psychological intervention (25), whereas in the rest of these studies (n=4) psychological interventions were more cost-effective (24, 45, 53, 56).

Combined interventions. Four studies assessed the cost-effectiveness of combined interventions (39, 41, 42, 55). Trauma-focused CBT and SSRI combination treatment was cost-effective in comparison with trauma-focused CBT alone, and CBT and SSRI combination treatment was cost-effective in comparison with usual care (39, 41). For both studies, combination therapy was cost-effective in comparison with the control conditions. Collaborative stepped care consisting of guided self-help, CBT, and antidepressants, dominated usual care (55), and another collaborative care intervention consisting of CBT components and pharmacotherapy also dominated usual care (42).

Discussion

Main findings

This study aimed at presenting an overview of the evidence regarding the cost-effectiveness of interventions for anxiety disorders. Furthermore, we appraised the quality of the studies included. Our study identified 42 full economic evaluations of interventions for treating anxiety disorders. All included studies with a CUA resulted in either a dominant ICER or an ICER below the WTP threshold of US$ 50,000 per QALY, meaning that the studied interventions were cost-effective in comparison with the control conditions. Generally, WTP thresholds are not available for clinical effect measures. Because the majority of the included studies were focused on GAD and PD, the findings of the current study do not cover the complete anxiety disorder spectrum and apply mainly to these two

anxiety disorders.

Heterogeneity in terms of interventions, (economic) study design, time horizon, outcome and study quality was high. Despite this heterogeneity, we categorized interventions into psychological interventions, pharmacological interventions, and combined interventions without specifying target groups and diagnoses. iCBT appeared to be a cost-effective internet-delivered intervention in comparison with the control conditions (3, 20, 22, 38, 51). In a previous review on the cost-effectiveness of internet-delivered interventions for mental health (10) it was concluded that guided internet-delivered interventions had favorable probabilities of being more cost-effective than various control conditions. This conclusion is supported by our findings. Four out of five studies comparing psychological treatment arms with pharmacological treatment arms showed that psychological interventions were more cost-effective in comparison with pharmacotherapy, which suggests that psychological interventions for anxiety disorders might be more cost-effective than pharmacological interventions.

Discussion of the results

The economic evaluations included used a variety of effect measures, which restricted comparability of the studies and their results. Few studies used both clinical effects and QALYs as outcome. Among the CEAs, the variety in outcomes was high due to the frequent use of diagnosis-specific measures. A generic outcome such as health-related quality of life (HR-QOL) does allow for comparison beyond a specific diagnosis. The frequent use of diagnosis-specific outcome measures in the identified economic evaluations could possibly be explained by the fact that it is under discussion whether HR-QOL as measured with the EQ-5D captures all relevant aspects of quality of life relevant for psychiatric patients (62). However, it is known that the EQ-5D is moderately responsive and valid for measuring HR-QOL in patients with anxiety disorders (63). Ideally, both clinical outcomes and generic HR-QOL outcomes are used in cost-effectiveness research.

The majority of the CUAs used the EQ-5D to derive utilities, but several studies used the SF and AQoL. Although these methods are multi-attribute utility assessments, Mihalopoulos et al. (64) showed that the AQoL, EQ-5D and SF are not equivalent. The use of different methods limits the comparability of these studies.

In accordance with the findings from an earlier review on the cost-effectiveness of interventions for anxiety disorders (4), we found that patients with PD and GAD were the most frequent target group within the identified economic evaluations, whereas patients with anxiety disorders such as specific phobias and OCD were considerably less

represented.

An important advantage of MBEEs is that they allow cost-effectiveness to be modelled over longer terms. However, only four out of 12 MBEEs with a time horizon beyond one year were identified (24-26, 39).

We categorized interventions into psychological interventions, pharmacological interventions, and combined interventions, but the specific interventions within these categories were still variable. In addition to the cost-effectiveness of intervention categories, it is also important to consider the cost-effectiveness of the specific interventions within these categories.

All included studies that analyzed the cost-effectiveness of pharmacological interventions were based on studies with GAD patients. Therefore, more research is needed in order to compare the cost-effectiveness results across different anxiety disorders. This is also the case for the psychological interventions. Although the studies that compared the cost-effectiveness of psychological interventions versus pharmacological interventions included populations with different anxiety disorders, too few studies were identified to determine whether the outcomes were moderated by diagnosis.

Quality assessment

The variability of the study quality was limiting in drawing firm conclusions regarding the cost-effectiveness of different types of interventions. Although the CHEC is a validated checklist for the quality assessment of economic evaluations, the assignment of scores is in part subjective. The sum score is not weighted. Aspects such as economic perspective, model structure, and model assumptions underlie other items. Therefore, a stronger weight for these items could be considered. Individual item scores should be considered in addition to the total score when interpreting study quality with the CHEC.

Strengths and limitations

One of the strengths of the current study is that standard methods for conducting and reporting systematic reviews were followed (11). Furthermore, psychological, medical, and health-economic literature databases were searched exhaustively. Another strength is that the quality of the studies included was appraised with the CHEC (15).

This study has also several limitations. Although this systematic review provides valuable information regarding existing evidence on the cost-effectiveness of interventions for anxiety disorders, aggregation of evidence is limited due to heterogeneity in terms of study design, study population, economic perspective, interventions, outcome measures, and

the cost categories included. This is considered to be a limitation since the heterogeneity of these characteristics may have influenced the ICERs. In addition, diagnostic criteria were not considered in this review, which might have increased the heterogeneity of the study populations as the severity of symptoms and anxiety varied across studies.

The vast majority of the studies were conducted in Western countries, which limits the generalizability of the results outside Western countries. Selection bias might have been introduced, as only articles written in English, German, or French were included.

Although we extracted the general cost categories included, such as healthcare costs and productivity costs, we did not specify the included costs within these categories. Types of healthcare costs might be different between studies, which limits the comparability and could affect cost-effectiveness results. The same holds for different methods that could have been applied when calculating productivity costs (human capital approach versus friction costs), although we expect this issue to be a minor concern due to the population considered (where absenteeism will be mainly short in duration) and the relatively short time horizon of most studies.

In general, studies with positive findings are more likely to be published than studies with negative findings. The possibility that positive findings are overrepresented in this systematic review was considered as a limitation.

Recommendations

The majority of the identified economic evaluations were directed on patients with PD and GAD. Specific phobias, OCD, and PTSD were underrepresented in the identified studies. Therefore, we think that more attention should be directed towards economic evaluations of interventions for these anxiety disorders as the current evidence on cost-effectiveness is mainly focused on GAD and PD.

The current review shows that the quality of the existing studies is variable. We therefore recommend that conducting high quality economic evaluations of interventions for anxiety disorders should be a research priority. High quality economic evaluations are necessary in order to draw solid conclusions about the cost-effectiveness of interventions for anxiety. Prioritizing interventions can thus be facilitated for decision makers.

Comparability of outcomes is essential for decision-making. More specifically, QALYs are preferred in addition to clinical effect measures because QALYs allow for comparison between the different types of anxiety disorders and other health conditions. In contrast to clinical effect measures, WTP thresholds are available for QALYs, which facilitates decision-making (65). In line with the prior recommendation, we suggest that future

economic evaluations on interventions of anxiety disorders should be designed, conducted, and reported in conformity with current guidelines for economic evaluation in order to increase comparability (66, 67).

Existing evidence on the cost-effectiveness of interventions for anxiety is based mainly on short term findings. Long term data could provide more insight in the societal cost-effectiveness since it is known that anxiety disorders are associated with high societal costs due to chronicity and productivity losses (2). Since it is not likely that short term findings capture these aspects, long term outcomes on cost-effectiveness are desirable.

The majority of the identified economic evaluations applied perspectives other than a societal perspective. A societal perspective is desirable because it is known that anxiety disorders are associated with substantial productivity losses. For healthcare payers, a societal perspective is less relevant. Therefore, studies could report cost-effectiveness from the healthcare and societal perspectives separately. Last, we advocate for a clear description and explanation of treatment alternatives in economic evaluations. In the identified MBEES, the treatment alternatives were generally poorly described. Usual care alternatives in particular require a clear explanation because the available mental healthcare is strongly region-specific and therefore not generalizable to other settings and countries. In order to overcome the issues discussed earlier, adherence to guidelines for economic evaluations is needed.

Conclusion

The current study provides an overview of all published full economic evaluations of interventions for anxiety disorders and on the quality of these evaluations. Psychological interventions might be more cost-effective in comparison with pharmacological interventions. iCBT in particular appeared to be cost-effective in comparison with the control conditions. Although numerous economic evaluations of interventions for anxiety disorders were identified, further conclusions on the cost-effectiveness of interventions could not be drawn due to heterogeneity in terms of interventions, (economic) study design, time horizons, and outcomes. Furthermore, the quality of the studies included was diverse.

Appendices available at www.rhophuis.com

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CHAPTER 3

Cost-effectiveness of falls prevention programs for older adults: A systematic review

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Abstract

Objectives. To provide a comprehensive overview of economic evaluations of falls prevention programs and to evaluate the methodology and quality of these studies.

Design. A systematic review of economic evaluations on falls prevention programs.

Setting. Studies (n=31) on community-dwelling older adults (n=25), on older adults living in residential care facilities (n=3), or on both populations (n=3), published before May 2017, were included.

Measurements. Information on study characteristics and health-economics was collected. Study quality was appraised using the 20-item Consensus on Health Economic Criteria.

Results. Economic evaluations of falls prevention through exercise (n=9), home assessment (n=6), medication adjustment (n=4), multifactorial programs (n=11), and various other programs (n=13) were identified. Approximately two-thirds of all reported incremental cost-effectiveness ratios (ICERs) with quality adjusted life-years (QALYs) as outcome were below the willingness-to-pay threshold of $50,000 per QALY. All studies on home assessment and medication adjustment programs reported favorable ICERs, whereas the results of studies on exercise and multifactorial programs were inconsistent. The overall methodological quality of the studies was good, although there was variation between studies.

Conclusion. The majority of the reported ICERs indicated that falls prevention programs were cost-effective, but methodological differences between studies hampered direct comparison of the cost-effectiveness of program types. The results imply that investing in falls prevention programs for older adults aged 60 years and older is cost-effective. Home assessment programs (ICERs <$40,000 per QALY) were the most cost-effective type of program for community-dwelling older adults and medication adjustment programs (ICERs <$13,000 per QALY) were the most cost-effective type of program for older adults living in a residential care facility.

Introduction

Fall-related injuries have a large impact on global health in older adults (1). Furthermore, consequences of fall-related injuries are associated with increased costs for medical consultation and treatment (2). The mean healthcare costs for an injurious fall treated at the emergency department are $11,450, and this amount increases with age (3). Almost two-thirds of all fall-related healthcare costs can be attributed to hospital and nursing home admissions (3). Studies have shown that exercise programs and programs combining multiple components, such as exercise and home assessment, effectively reduce fall-related injuries in older adults (4-7). Although effective falls prevention programs exist, the occurrence of falls among older adults is still high. Because financial resources in healthcare are limited, it is important that policy-makers invest in the implementation of cost-effective falls prevention programs. An up-to-date overview of all published economic evaluations of falls prevention programs and their methodological quality is relevant as the results can inform policy decisions. Previous systematic reviews of economic evaluations of fall prevention programs have shown that programs consisting of home visits (8), and those consisting of strength and balance exercises (9) are cost-effective. Davis et al. (2010) published a comprehensive overview of economic evaluations of falls prevention programs, which was limited to community-dwelling older adults (9). Since that publication, 22 new economic evaluations of falls prevention programs have been published. Therefore, an update is deemed relevant. The aim of this review is to provide a comprehensive overview of economic evaluation studies on falls prevention programs among community-dwelling older adults and older adults living in a residential care facility, and to evaluate the study designs, health-economic characteristics, outcomes, and methodological quality of these studies. This review is focused on a broader population and it makes a distinction between community-dwelling older adults and older adults living in a residential care facility. Furthermore, the results are compared with common WTP thresholds, as this is the next step in an informed decision-making process.

Methods

The methods and reporting of this systematic review are in concordance with the PRISMA statement (10). The study protocol is registered in the PROSPERO register (number CRD42017071726).

Literature search

Relevant studies were identified through systematic literature searches in several databases. The search strategies were developed in consultation with an information specialist. Reference lists and citation indices of the included papers were inspected to identify additional relevant studies. Searches were restricted to English-language papers that were published in peer-reviewed journals before May 2017.

Study selection

This study included trial-based economic evaluations (TBEEs) and model-based economic evaluations (MBEEs) (11). In TBEEs, a cost-effectiveness study is conducted alongside an effectiveness trial. Available evidence is used to estimate the cost-effectiveness of programs in MBEEs. Only studies in which both costs and effects of two or more programs were compared by means of an incremental cost-effectiveness analysis were included (11). Cost-effectiveness analyses (CEAs), cost-utility analyses (CUAs), and cost-benefit analyses (CBAs) were considered for inclusion. In a CEA, costs and clinical effects (e.g., falls prevented) are used as outcome, whereas costs and generic utility measures are used as outcome in a CUA. QALYs are generally used as a generic utility measure in a CUA. In a CBA, costs and effects of programs are both expressed in monetary terms yielding net monetary benefits. For this review, only studies on adults aged 60 years and older were included. The results of studies on community-dwelling older adults and older adults living in a residential care facility are reported separately in this review. Studies that were primarily focused on fracture prevention were excluded.

Data extraction

After deletion of duplicate studies, one reviewer (BO) screened the titles and abstracts of the remaining studies. A second reviewer (RO) screened a subset of the titles to check for consistency. Two reviewers (BO/RO) independently read the full text of the studies included. After non-eligible studies were excluded, relevant study characteristics and health-economic data were retrieved for analysis (BO/RO). When the health-economic perspective or baseline fall risk was not reported in an article, the perspective and/or baseline fall risk was derived from the methods or results section of the article (BO/RO). The data extraction was independently checked by a second reviewer (BO/RO). A third reviewer (SP) was involved for resolving discrepancies.

Outcome

The primary outcome measure was the incremental cost-effectiveness ratio (ICER). An ICER is a standard outcome in economic evaluations and is expressed as the additional costs per unit of outcome gained for the intervention compared to usual care. The outcome as defined in the individual studies is reported. In case an ICER was not reported, but a full economic evaluation was performed, the health-economic results were reported descriptively. In order to compare price levels between countries, all ICERs were converted to 2016 US$ by using purchasing power parity rates and the Consumer Price Index (12, 13). In order to maintain comparability of the results of the included CUAs with QALY as outcome, a willingness-to-pay (WTP) threshold of US$ 50,000 per QALY gained was applied, which is a widely accepted threshold in the US (14). Because the threshold of $50,000 has been in use since the 1980s, we have used this as a lower boundary, and the outcomes were compared with a commonly used inflation-adjusted threshold of $100,000 per QALY (15). The WTP threshold is the maximum amount society is willing to pay for gaining one additional QALY. When the ICER is lower than the threshold, the program is considered cost-effective in comparison with the control condition. The ICERs of CEAs were not compared with a threshold, as generally accepted thresholds do not exist for outcomes other than QALYs.

Quality assessment

In concordance with the Cochrane collaboration guidelines (16), the quality of the studies was assessed with the extended Consensus on Health Economic Criteria (CHEC) (17). The CHEC contains 20 items covering internal and external validity of economic evaluation studies. Each item on the CHEC checklist was scored with 'No' (0), 'Suboptimal' (0.5), 'Yes' (1), or 'NA', as described by Ophuis et al. (18). The sum score (%) for each study was reported in this review. The quality of the studies was assessed and scored independently by two reviewers (BO and RO). A third reviewer (SP) was involved for resolving discrepancies. The correlation between the total quality scores and ICERs are expressed in a Pearson's correlation coefficient, Separate correlation coefficients were calculated for CUAs, CEAs, falls prevention program type, and population. The critical p-value was set at 0.05.

Results

Literature search and study selection

The literature search yielded 5,209 studies. After removing duplicates, the titles and abstracts of 3,063 studies were screened for relevance. This resulted in the exclusion of 2,980 studies for the following reasons: not primarily focused on falls prevention programs, and no economic evaluation. Eighty-three studies were read in full-text for eligibility assessment. Fifty-four studies were excluded for the following reasons: no full economic evaluation (n=32), no original research (n=11), population aged under 60 years (n=6), and protocol article (n=5). Two additional studies were identified through scanning the reference lists of included studies included. Thirty-one studies were included in the systematic review (Figure 1).

The studies included were published between 1996 and 2017. The study populations were community-dwelling older adults (n=25), older adults living in a residential care facility (n=3), or both populations (n=3). The following falls prevention programs were identified: exercise (n=9), home assessment (n=6), medication adjustment (n=4), multifactorial programs (n=11), and other programs (n=13). Most of the studies compared falls prevention programs with usual care or no program. The number of falls prevented and QALYs were mainly used as outcome. The study characteristics are reported in appendix 2.1.

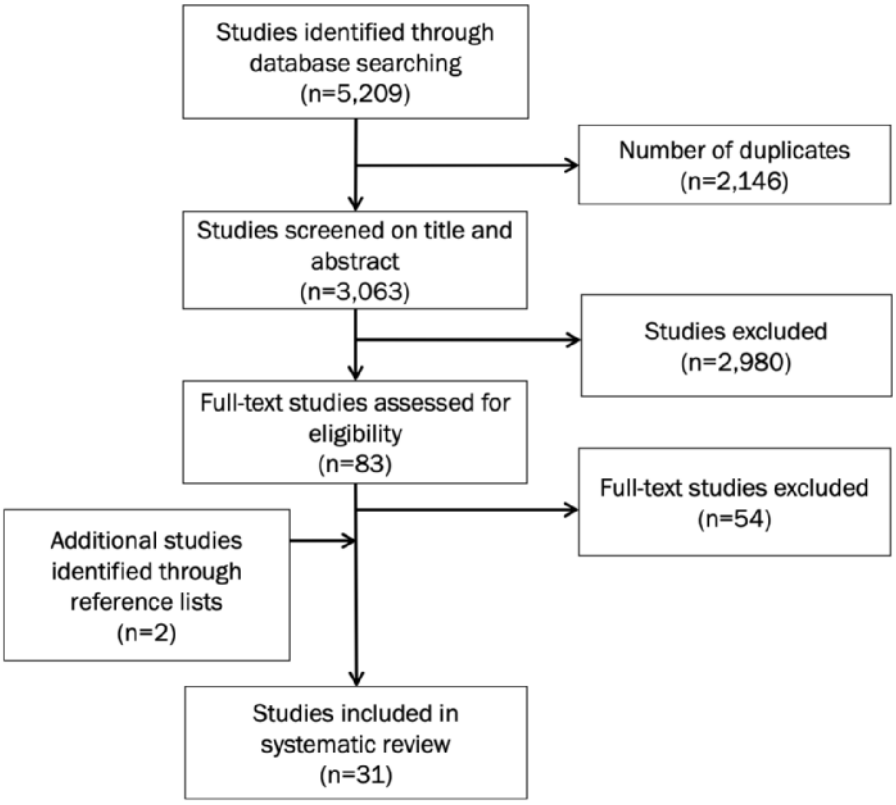

Figure 1: Flowchart of search for studies of cost-effectiveness of falls prevention programs for older adults

Quality assessment

Quality scores ranged from 62% to 97% (Table 1). The average score of 84% shows that the overall methodological quality was good. The quality of the studies on home assessment and medication adjustment programs had the lowest scores on average (82%); whereas exercise and other programs had the highest scores (88%). The studies reporting a cost saving or cost-effective falls prevention program had an average score of 83%. Studies that did not report a cost saving or cost-effective program scored 91% on average. There was no significant correlation between the quality score and the reported ICERs for CUAs ($r(44)=-0.04$, $p=0.808$) and CEAs ($r(44)=-.14$, $p=0.366$). The association remained non-significant when the correlation analysis was performed for program type and population.

Table 1: CHEC quality assessment items and scores, subdivided by falls prevention program

Authors, year	Quality score (%) [1]
Exercise programs	
Church et al. 2011	83
Church et al. 2012	83
Davis et al. 2011	89
Farag et al. 2015	92
McLean et al. 2015	95
Munro et al. 2004	72
Robertson et al. 2001 (1)	94
Robertson et al. 2001 (2)	91
Robertson et al. 2001 (3)	91
Average	*88*
Home assessment programs	
Campbell et al. 2005	78
Church et al. 2012	83
Pega et al. 2016	83
Sahlen et al. 2008	84
Salkeld et al. 2000	85
Smith et al. 1998	76
Average	*82*
Medication adjustment programs	
Church et al. 2011	83
Church et al. 2012	83
Church et al. 2015	93
Frick et al. 2010	68
Average	*82*
Multifactorial programs	
Church et al. 2011	83
Church et al. 2012	83
Church et al. 2015	93
Farag et al. 2014	75
Heinrich et al. 2013	86

Hendriks et al. 2008	89
Irvine et al. 2010	92
Jenkyn et al. 2012	79
Müller et al. 2014	83
Peeters et al. 2011	92
Rizzo et al. 1996	62
Average	*83*
Other programs	
Church et al. 2011	83
Church et al. 2012	83
Church et al. 2015	93
Lee et al. 2013	90
Patil et al. 2016	97
Poole et al. 2015	75
Sach et al. 2007	89
Cockanye et al. 2017	63
Mori et al. 2017	93
Van Haastregt et al. 2013	94
Average	*86*

[1] Score expressed as percentage of the maximum score.

Economic evaluations

Nineteen studies performed a CUA with QALYs as outcome. In the majority of these studies, QALYs were calculated by multiplying utility values by the remaining life years corresponding to the time horizon of the studies. Thirteen studies used utility values that were derived from the EQ-5D. One study used the SF-36, and one study used the EQ-5D and SF-36. Three studies did not report how utility values were derived. A societal perspective (n=13) was applied as often as a healthcare perspective (n=13) (appendix 2.2). All studies with a healthcare perspective included program costs and other healthcare costs in their analyses (appendix 2.3-2.4). Nineteen trial-based economic evaluations (TBEEs) and twelve model-based economic evaluations (MBEEs) were

identified. The most commonly applied time horizon among TBEEs was one year (58%), followed by two years (11%). Among the MBEEs, the most commonly applied time horizon was a lifetime horizon (50%). Ten TBEEs (53%) applied bootstrapping in order to deal with sampling uncertainty. The main cost-effectiveness findings of this review were subdivided by program type (appendix 2.2).

Figure 2 provides a graphical overview of all reported ICERs in the CUAs, subdivided by program type. In this figure, a distinction was made between community-dwelling older adults and older adults living in a residential care facility. In total, about two-thirds of the ICERs with QALYs as outcome were below the WTP threshold of $50,000 per QALY (Figure 2), and 86% of the ICERs were below the threshold of $100,000 per QALY. All ICERs of home assessment and medication adjustment programs were cost-effective given both thresholds. Half of the reported ICERs of exercise programs and multifactorial programs and over two-thirds of the reported ICERs of various other programs indicated that these programs were cost-effective when a threshold of $50,000 per QALY is applied. However, all ICERs of exercise programs and the vast majority of the ICERs of multifactorial programs were below the threshold of $100,000 per QALY.

Figure 3 presents all reported ICERs with falls as outcome. The majority of the ICERs of exercise programs, and all ICERs of medication adjustment programs were below $2,000 per fall prevented (Figure 3). In contrast, most of the ICERs of multifactorial programs were higher than $2,000 per fall prevented.

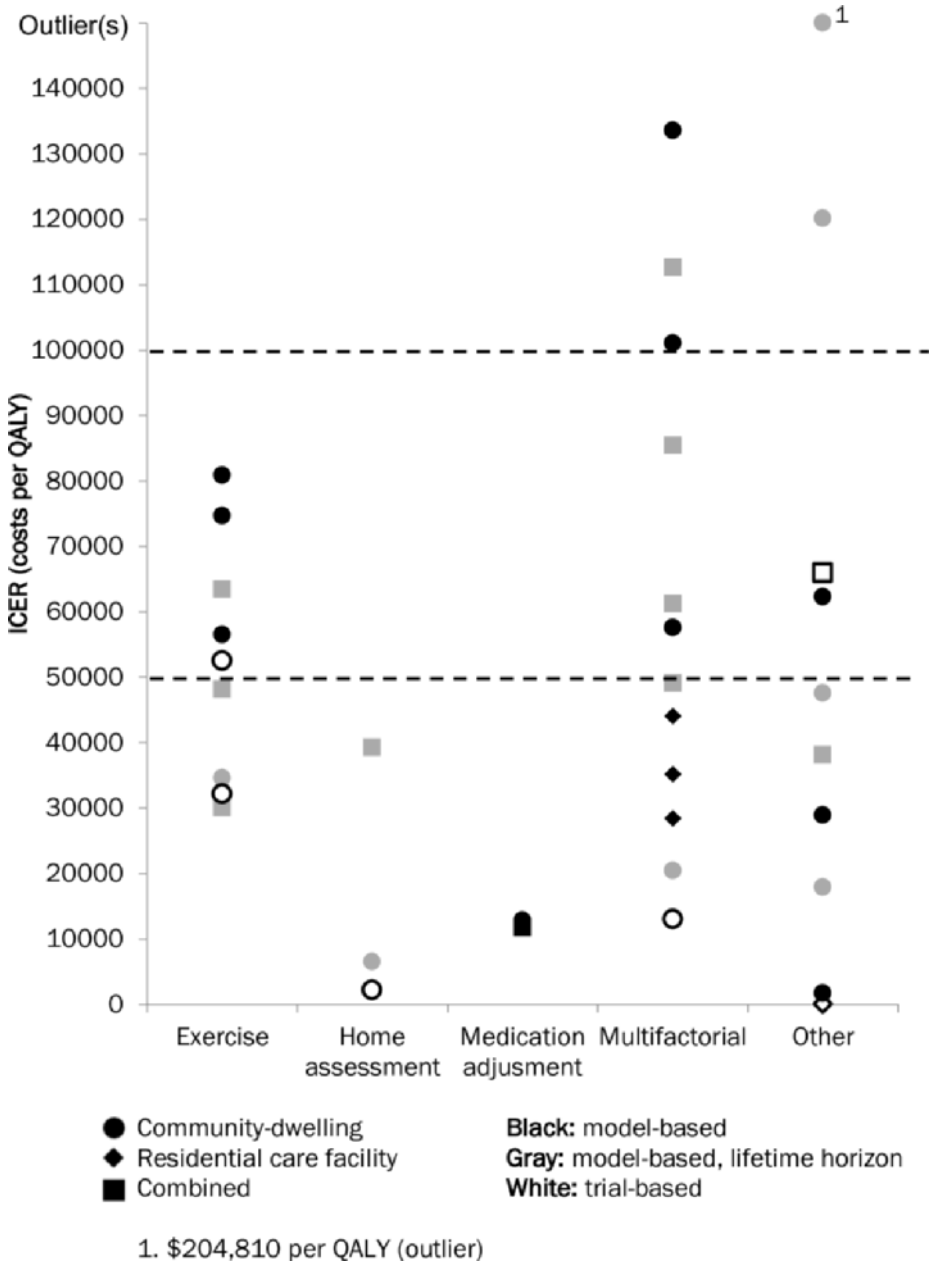

Figure 2: Overview of incremental cost-effectiveness ratios (ICERs) per falls prevention program, with costs per quality-adjusted life year (QALY) gained as outcome (cost-saving ICERS excluded)

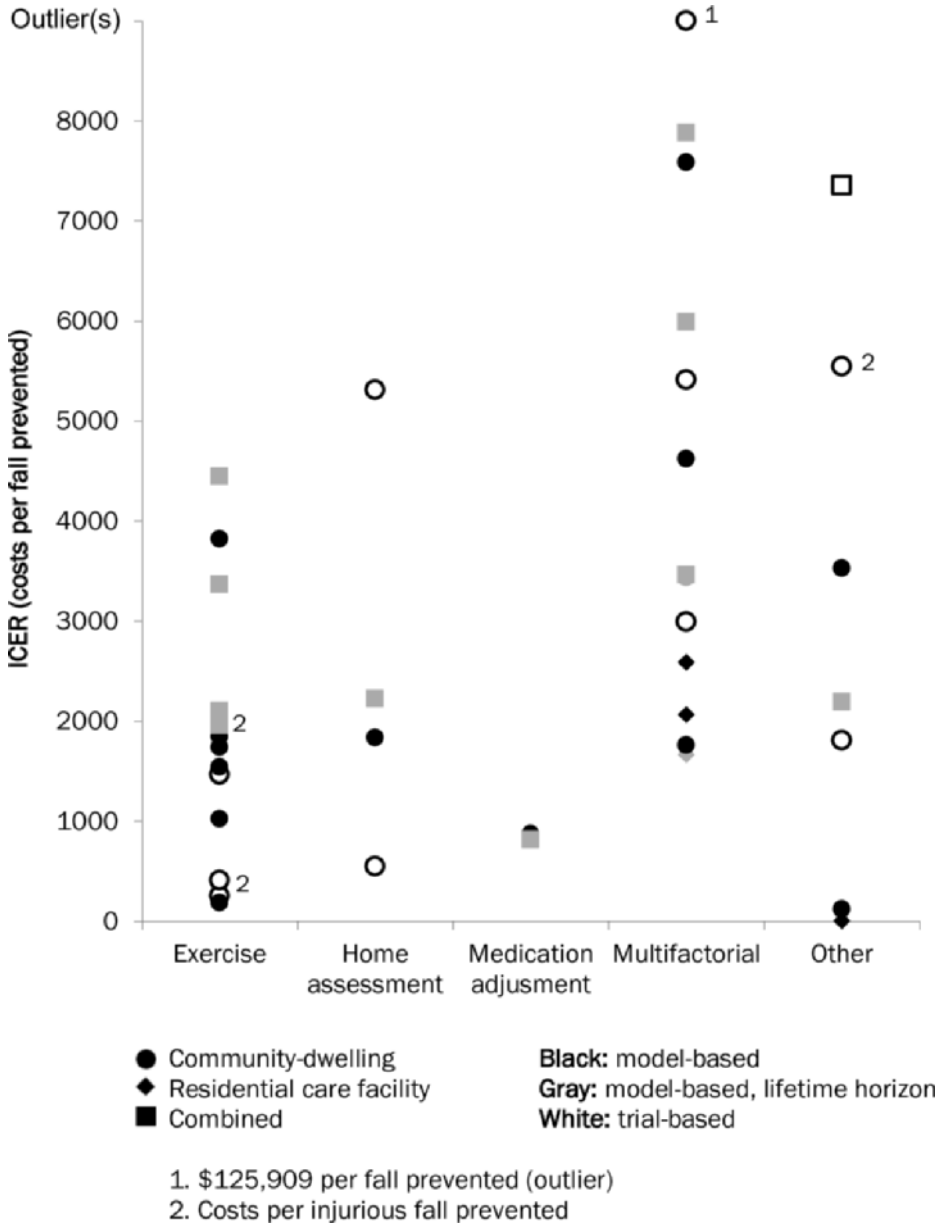

Figure 3: Overview of incremental cost-effectiveness ratios (ICERs) per falls prevention program, with costs per fall prevented as outcome (cost-saving ICERS excluded)

Exercise programs. Nine economic evaluations of exercise programs were identified (19-27). The ICERs of CUAs ranged from $30,013 to $80,860 per QALY. Six ICERs of CUAs were cost-effective based on a threshold of $50,000 per QALY and of $100,000 per QALY. Davis et al. (2011) reported that once-weekly resistance training and twice-weekly resistance training were cost saving in comparison with twice-weekly balance and tone classes (21).

The ICERs of CEAs on exercise programs ranged from $186 to $4,446 per (injurious) fall prevented. Robertson et al. (2001) reported relatively low ICERs of CEAs for older populations (≥75) (25-27). Church et al. (2011, 2012) showed that Tai Chi and group-based exercise in a high-risk population were the most cost-effective programs (19, 20).

Home assessment programs. Economic evaluations of home assessment programs were performed in six studies (20, 28-32). The ICERs of CUAs ranged from $2,158 to $39,281 per QALY and were all below thresholds of $50,000 and $100,000 per QALY.

The ICERs of CEAs ranged from $548 to $5,313 per fall prevented. The studies with an older population (≥75) reported lower ICERs than the studies with a younger population (≥65).

Medication adjustment programs. Four economic evaluations of medication adjustment programs were identified (19, 20, 33, 34). Church et al. (2011,2015) reported the ICERs of CUAs on medication review or withdrawal and showed that it was cost saving in a population of older adults living in a residential care facility (19, 33). Furthermore, Church et al. (2012) showed that the program was cost-effective in community-dwelling older adults (20). Frick et al. (2010) compared the ICERs of CUAs of a medication adjustment program with exercise, home assessment, multifactorial, and vitamin D programs and reported that medication adjustment was the least expensive and most effective program in community-dwelling older adults (34). The studies by Church et al. also showed relatively low or cost saving ICERs of CEAs on a medication review and withdrawal program (19, 20, 33).

Multifactorial programs. Eleven studies performed an economic evaluation of multifactorial programs (19, 20, 33, 35-42). The ICERs of CUAs ranged from $20,427 to $112,598 per QALY. Seven out of fourteen ICERs were below the threshold of $50,000 per QALY, and ten were below $100,000 per QALY. Two studies reported that their program in community-dwelling older adults (≥65) was less effective and costlier than the

control condition (37, 41).
The ICERs of CEAs ranged from $1,666 to $125,909 per fall prevented. The ICERs were lower in a population living in a residential care facility than in a community-dwelling population. Furthermore, in both populations, a program consisting of the modification of risk factors, information sessions, and follow-up had the lowest ICERs.

Other programs. Economic evaluations of a variety of other falls prevention programs (vitamin D, cataract surgery, cardiac pacing, podiatry care, bisphosphonates and exercise, and cognitive behavioral therapy) were reported in thirteen studies (19, 20, 33, 43-49). Eleven ICERs of CUAs were reported in these studies, of which seven programs were cost saving or cost-effective (19, 20, 33, 43, 47). However, nine were cost-effective given a threshold of $100,000 per QALY. Mori et al. (2017) showed that with an increase in age, the costs per QALY decreases (45). Additional information on the other programs can be found in appendix 2.2.

Discussion

This systematic review provides a comprehensive overview of the results of 31 economic evaluations on falls prevention programs among community-dwelling older adults and older adults living in a residential care facility. In general, medication adjustment programs and home assessment programs showed the most favorable results because the lowest ICERs were reported for these program types. However, when a higher WTP threshold of $100,000 is applied, the majority of the remaining program types (exercise, multifactorial, and other) were also cost-effective. Given the earlier published review by Davis et al. (2010) (2), it appears that medication adjustment programs and vitamin D supplementation and cataract surgery are also falls prevention programs that are potentially cost saving. Direct comparison of the relative cost-effectiveness between program types was hampered by the methodological differences between the studies. The majority of the TBEEs were powered for falls and not for costs. This may have contributed to the heterogeneity of the results, as costs often have a very skewed distribution (9).
It should be noted that these findings are mainly based on CUAs because there is no generally accepted cost-effectiveness threshold for the costs per fall prevented.
This review shows that home assessment programs were the most cost-effective type of program for community-dwelling older adults. Medication adjustment programs were the most cost-effective type of program for older adults living in a residential care facility. The

results for mixed populations were more inconsistent, but for higher WTP thresholds exercise, home assessments, and medication adjustment programs were all cost-effective. In general, multifactorial programs and other programs were less favorable, but it should be noted that these programs were more frequently assessed than home assessment and medication adjustment programs. Namely, multifactorial programs were assessed eleven times and other programs were assessed thirteen times; whereas, when combining home assessment and medication adjustment programs, ten assessments were made. This could have contributed to a wider range of results. A possible explanation for the less favorable cost-effectiveness results for exercise and multifactorial programs is that the program costs for these programs are likely to be higher than the program costs for home assessment and medication review programs. Home assessment and medication review programs are often one-time only programs, whereas exercise and multifactorial programs consist of multiple classes or appointments. A difference in health-economic perspective or baseline fall risk between studies could have contributed to differences in cost-effectiveness results as well.

The cost-effectiveness of interventions depends on the WTP threshold. For this study WTP thresholds of $50,000 and $100,000 for one QALY gained were applied, but WTP values in general have no solid scientific basis (50). Choosing a relevant WTP threshold is essential for policy-making, as the inappropriate use of WTP thresholds might lead to inappropriate decisions. For example, the cost-effectiveness of falls prevention programs severely decreases when a lower threshold of $20,000 per QALY is applied. In this case, the majority of the ICERs reported are above the threshold. Conversely, the cost-effectiveness increased substantially when a higher threshold of $100,000 was applied.

Studies performed on older adults living in a residential care facility reported slightly more favorable ICERs than studies performed on community-dwelling older adults. However, it is not warranted to conclude that falls prevention programs are more cost-effective among adults living in a residential care facility, as only three studies were performed in these populations. Additional research is needed in order to properly compare the results for different populations in economic evaluations of falls prevention programs.

Studies on older populations reported more favorable ICERs than studies on younger populations. However, 90% of the ICERs of CUAs originated from studies on older adults aged 65 to 75 years old whereas 10% of the ICERs originated from studies on older adults over the age of 75 years. Therefore, one is unable to draw firm conclusions about age differences. A possible explanation for the observed differences between age groups is that older people are more likely to fall (51). More falls can thus be prevented as a result

of a prevention program. Older people are also more often hospitalized after fall-related injury, which is associated with high healthcare costs (51). Consequently, more costs could be saved among older people.

Relevant study quality differences between falls prevention program types could not be identified. On average, studies reporting a cost saving or cost-effective falls prevention program had lower quality scores than studies not describing a cost-effective falls prevention program (83% versus 91%), but the difference was small and therefore not likely to be influential.

One of the strengths of this review is that standardized methods for conducting and reporting systematic reviews were followed. All reported ICERs were converted to 2016 US$ which allows for comparison between cost data. Differences resulting from purchasing power and inflation were eliminated. Another strength of this study is the extensive health-economic quality assessment.

This review also has several limitations. Although WTP thresholds differ between countries, the same two WTP thresholds were applied for all CUAs. Selection bias might be present because the search was limited to English-language papers that were published in peer-reviewed scientific journals. In determining the overall cost-effectiveness of home assessment and medication adjustment programs, the effectiveness of these programs has to be taken into account as well. Reviews have shown that the evidence on the effectiveness of these programs is fairly inconsistent (4, 6). Publication bias in economic evaluations is likely to be present, as economic evaluations are less likely to be performed when an intervention is ineffective (52). Therefore, the findings presented in this review are likely to overestimate the cost-effectiveness of falls prevention programs in general.

Future economic evaluations of falls prevention programs should be designed, conducted, and reported in accordance with the current guidelines for economic evaluations in order to increase comparability, which is essential for informing decision-making (53, 54). In addition, comprehensive cost-effectiveness models comparing multiple falls prevention programs such as described by Church et al., provide insight into the relative cost-effectiveness of different program types within the same population (19, 20, 33). Furthermore, QALYs are preferred as outcome in addition to clinical effect measures as QALYs can be compared with established WTP thresholds. Comparing the QALYs in this review with two WTP thresholds shows that the majority of falls prevention programs are cost-effective. Moreover, some studies show that falls prevention is effective while costs can be saved. Thus, decision makers should consider implementing falls prevention

programs, also taking the increasing impact of fall-related injuries among older adults into account. Future studies should clearly report whether they target high-risk, low-risk, or mixed populations as the baseline fall-risk is an important driver for cost-effectiveness (2). This is important for identifying whether falls prevention programs are more cost-effective for certain risk groups because some studies reported more favorable results for older adults with a higher fall risk.

This review implies that investing in falls prevention programs for adults aged 60 years and older is cost-effective, which particularly applies to home assessment for community-dwelling older adults and medication adjustment programs for older adults living in residential care facilities. Moreover, programs are found to be more cost-effective as the age of participants increases.

Appendices available at www.rhophuis.com

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CHAPTER 4

Prevalence of post-traumatic stress disorder, acute stress disorder and depression following violence related injury treated at the emergency department: A systematic review

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Abstract

Background. In order to gain insight into the health impact of violence related injury, the psychological consequences should be taken into account. There has been uncertainty regarding the prevalence of posttraumatic stress disorder (PTSD), acute stress disorder (ASD), and depression among patients with violence related injury. An overview of prevalence rates may inform our understanding of both prognosis and recovery for these patients. Therefore, we aim to provide an overview of the published literature reporting the prevalence rates and trajectories of PTSD, ASD, and depression following violence related injury, and to assess the quality of the studies included.

Methods. A systematic review was conducted in order to provide an overview of the published literature reporting the prevalence of PTSD, ASD and depression following violence related injury treated at the emergency department or hospital. The EMBASE, MEDLINE, Cochrane Central, PubMed, and PsycINFO databases were searched systematically. The quality of the included studies was assessed.

Results. We included sixteen studies reporting the prevalence rates of PTSD, ASD, or depression. Clear prevalence trajectories could not be identified because the range of prevalence rates was diverse at each time point. Heterogeneity resulting from the use of different diagnostic instruments limited comparability. The included studies were susceptible to bias due to low response rates and loss to follow-up.

Conclusions. The differences in diagnostic instruments limited comparability of the prevalence rates. Therefore, clear prevalence trajectories could not be identified. Study participation and loss to follow-up require more attention in future studies. Uniformity in diagnostic procedures is needed in order to draw general conclusions on the prevalence of PTSD, ASD, and depression following violence related injury.

Background

More than 1.5 million people worldwide die from violence related injury every year, and even more people suffer from non-fatal injury caused by violence (1). Approximately 1.4 million non-fatal violence related injuries are treated annually in hospital emergency departments (ED) in the US (2). In Western Europe, 670,000 violence related injuries require medical treatment each year (3). According to the diagnostic and statistical manual for mental disorders (DSM), exposure to serious injury is an example of a traumatic event (4). Longitudinal studies of responses to traumatic events show that mental disorders such as post-traumatic stress disorder (PTSD), acute stress disorder (ASD), and depression frequently occur after experiencing a traumatic event, although the course can be variable (5).

PTSD and ASD are trauma and stressor-related psychiatric disorders that could occur after experiencing or witnessing events involving physical injury, death, or other threats to the physical integrity (4). Re-experience of the traumatic event and avoidance of trauma-related stimuli are the main symptoms of trauma and stressor-related disorders (4). Unlike PTSD and ASD, depression is a mental disorder that is not directly linked to a traumatic event. However, substantial depression prevalence rates have been reported among patients who experienced a traumatic event such as interpersonal violence (6, 7). A depressive episode is characterized by a constant depressed mood, loss of interest, or loss of pleasure (4).

A systematic review by Santiago et al. (5) reported that PTSD trajectories differ between patients exposed to intentional and non-intentional traumatic events. The PTSD prevalence among patients exposed to non-intentional traumatic events decreased in time, whereas the prevalence among patients exposed to intentional traumatic events increased. This might suggest that the PTSD trajectory of patients with violence-related injury differs from patients with non-intentional injury. However, Santiago et al. (5) also included studies on victims of terroristic attacks, war, and hostage situations in their systematic review. These participants did not necessarily sustained injury. It therefore remains unclear what the specific trajectories are for patients with violence related injury. Furthermore, little is known about the prevalence and trajectories of ASD and depression in this specific population.

In order to gain insight into the total health impact of injury following violence, the psychological consequences should be taken into account given the high prevalence rates of PTSD, ASD, and depression that have been reported post-injury (5, 8-10). This paper

provides PTSD, ASD, and depression prevalence estimates among patients with violence related injury, which may inform our understanding of both prognosis and recovery for these patients. An overview of prevalence rates provides insight into the public health treatment needs. Targeted interventions can be provided when the PTSD, ASD and depression trajectories of patients who sustained violence related injury are known. Therefore, we aim to (1) provide an overview of the published literature reporting the prevalence rates and trajectories of ASD, PTSD, and depression following violence related injury, and (2) to assess the quality of the studies included.

Methods

In order to identify studies reporting the prevalence rates of ASD, PTSD, and depression among patients who sustained violence related injury, a systematic literature review was conducted. The methods and reporting of this systematic review are in concordance with the PRISMA statement on reporting standards for systematic reviews (11). The study protocol is registered in the PROSPERO international prospective register of systematic reviews (registration number CRD42016043167).

Literature search

Relevant studies were identified through systematic literature searches in the EMBASE, MEDLINE, Cochrane Central, PubMed, and PsycINFO databases. The search strategies were developed in consultation with a medical librarian. A detailed description of the search strategy can be found in appendix 3.1. Reference lists and citation indices of the included papers were inspected to identify additional relevant citations. We restricted searches to English-language papers, published in peer-reviewed journals before November 2017.

Study selection

Studies reporting the prevalence of PTSD, ASD, or depression after ED or hospital treated injury following interpersonal violence were included in this review. We defined the following inclusion and exclusion criteria:

Participants. Studies were included if the injury was intentionally caused by another person or persons, such as (sexual) assault or stabbing. Studies on violent incidents that not necessarily involve injury, such as hostage situations or witnessing terroristic attacks, were excluded. Studies on a mixed population, e.g. all trauma patients, were only included

if they reported separate prevalence rates for injury caused by intentional violence (excluding self-harm). We only included studies on patients who have been treated at the ED or hospital in order to maintain comparability in terms of injury severity. We did not apply restrictions on countries or regions in which studies were conducted. Studies on adults, children, and adolescents were included.

Outcome. We included studies in which the prevalence rates of PTSD, ASD or depression were reported directly or indirectly (i.e. by reporting the number of cases and the total number of patients) by means of a validated questionnaire or diagnostic interview. We applied the case definitions and diagnostic thresholds as reported in the individual studies.

Study design. Prospective and retrospective cohort studies, longitudinal studies, cross-sectional studies, time series, and clinical trials were included. We excluded reviews, qualitative studies, case reports, editorials, and study protocols.

Data extraction

Titles and abstracts of all identified studies were screened for relevance by one reviewer (RO, BO, or JH). After initial selection, the remaining records were independently read in full-text by two reviewers (RO and BO) for the eligibility assessment. Discrepancies were discussed and resolved by consulting a third reviewer (JH). Two reviewers (RO and BO) extracted data on the study populations, study setting, injury details, prevalence rates, diagnostic instruments, and follow-up. If possible, we provided prevalence rates at different points in time. We used approximations when specific time points were not reported. For example, when 'within two weeks after ED admission' was reported as time indication, the midpoint (one week) was used. We reported gender-specific prevalence rates and measures of injury severity if provided.

Quality assessment

A quality assessment in terms of risk of bias was performed with the Quality in Prognosis Studies (QUIPS) tool (12), which was developed for assessing the risk of bias of prognostic studies. Although the current systematic review does not focus on prognostic studies, we used the QUIPS tool because it covers general quality criteria on risk of bias. We considered these general criteria as appropriate because of the variety of study designs included in our study. The following domains of the QUIPS were selected in order to assess

the risk of bias: study participation, study attrition, outcome measurement, and statistical analysis. Two reviewers (RO and BO) independently used the QUIPS tool to assess the risk of bias. Each domain was scored as 'low risk', 'moderate risk' or 'high risk'. Any discrepancies in the domain scores were resolved via discussion until consensus was reached.

Results

Literature search

In total, the literature search yielded 3,556 articles. After excluding 1,537 duplicates, the titles and abstracts of 2,019 articles were screened for relevance. The screening of titles and abstracts resulted in the exclusion of 1,979 articles. Forty studies were left for full-text eligibility assessment, of which 24 were excluded for several main reasons: no prevalence reported, no violence related injury, no ED or hospital admission, literature review. Finally, sixteen studies were included in the systematic review. A flow chart of the study identification process is presented in Figure 1.

Study characteristics

The majority of the studies were conducted in the United States (n=10) (13-22) (Table 1). The remaining studies were conducted in the United Kingdom (n=3) (23-25), Denmark (n=1) (26), and Norway (n=2) (27, 28). Seven studies included patients aged eighteen years and older (14, 20-22, 26-28) and two studies included patients aged sixteen years and older (23, 25). In two studies (13, 24), the age of the participants was not specified. The remaining five studies applied different age criteria (Table 1) (15, 19).

All studies included patients who presented to the ED, trauma center, or hospital with injury following intentional violence. Alarcon et al. (13) included patients with the ICD-9-CM injury codes 800-995, covering injury such as open wounds and fractures. Injury related to sexual assault was excluded in three studies (14, 15, 19) and injury caused by domestic violence was excluded in four studies (19, 24, 27, 28). In four studies on children and adolescents, injury caused by child abuse was excluded (15, 16, 18, 19).

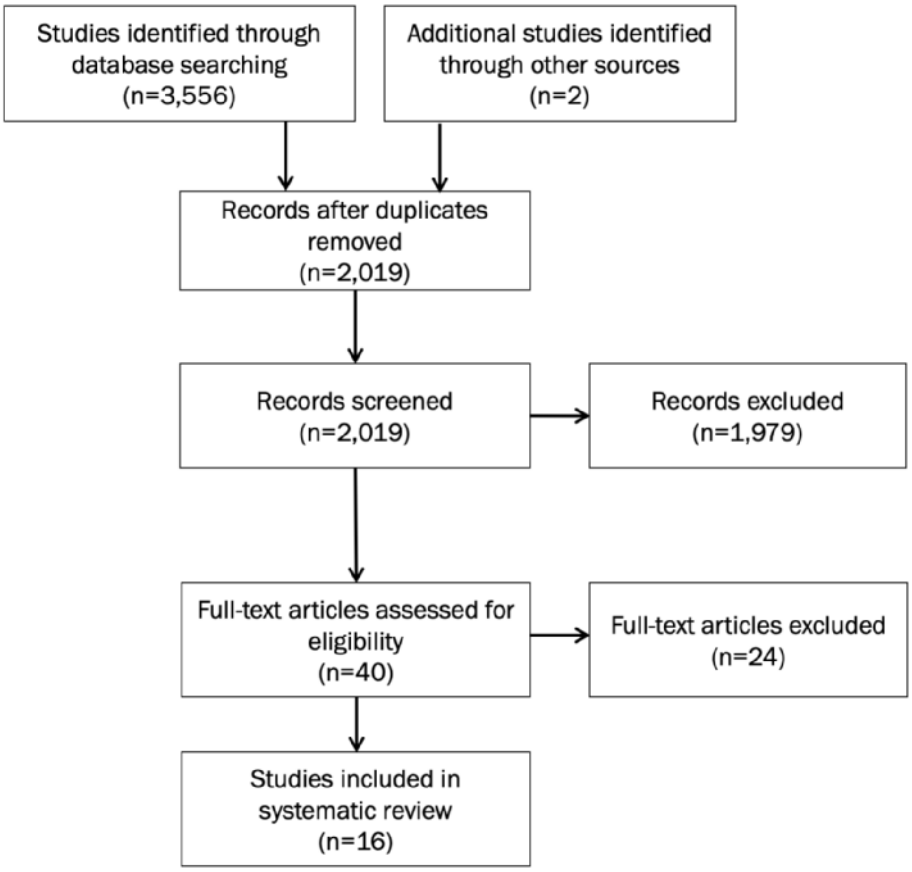

Figure 1: Flow chart of the study identification process

Diagnostic instruments

A full structured clinical interview was used as diagnostic instrument in four out of sixteen studies (15, 20, 22, 24). All DSM IV or V diagnostic criteria for PTSD (n=4) and depression (n=1) were met in these studies (Table 2). The Child and Adolescents Trauma Survey for assessing PTSD symptoms was used as diagnostic instrument in two studies (16, 18). In both studies, patients were considered having PTSD when they scored 27 or higher. The Immediate Stress Response Checklist for ASD was used in the same studies (16, 18), although one of these studies did not report a cut-off score (18). The diagnostic instruments used in the other studies were all different from each other. Twelve out of sixteen studies (75%) used brief questionnaires based on self-report or screening measures to obtain probable diagnoses. Therefore, these studies may have included individuals who would not have met the diagnostic criteria for ASD, PTSD, or depression if

a full diagnostic interview would have been conducted. Brief questionnaires are mainly focused on symptoms whereas in a full diagnostic interview impairment is assessed as well.

Prevalence rates

The PTSD, ASD, and depression prevalence rates at different points in time are reported in Table 2. Fifteen studies reported the prevalence of PTSD following violence related injury (13, 15-28), five studies reported the prevalence of ASD (14, 16, 18, 24, 26), and five studies reported the prevalence of depression (14, 15, 17, 18, 21). The PTSD prevalence at 1, 3, 6, and 12 months post-injury ranged between 11.0-60.9%, 5.8-30.4%, 1.9-23.9%, and 16.3-27.1% respectively. The following range of ASD prevalence rates were reported <1 week post-injury and 1-2 weeks post-injury: 24.0-24.6% and 11.7-40.6%. Four studies reported depression prevalence rates <1 month post-injury ranging between 3.0% and 35.3%. Beyond one month post-injury, a prevalence rate of 16.8% was reported. Heterogeneity resulting from the use of different diagnostic instruments strongly limited the comparability of the reported prevalence rates of PTSD, ASD, and depression. In total, one study reported injury severity of the target population (26) and one study reported gender-specific prevalence rates (27) (Table 2).

Table 1: Overview of the study characteristics reporting the prevalence of ASD, PTSD, or depression following violence related injury

Authors, year, country, ref.	Study population	Setting details	Violence and injury details	Disorder	DSM criteria [1]
Alarcon et al., 2012, USA, (13)	Injured patients treated at the ED, age not specified	Urban level I trauma center	Assault	PTSD	No
Bisson et al., 2010, UK, (23)	Patients aged over 16 years, treated at the ED following physical assault	ED	Assault	PTSD	No
Boccelari et al., 2007, USA, (14)	Patients aged 18 years and older who are victims of violent crime treated at the ED, with and without hospitalization	Urban hospital	All types of violence, sexual assault excluded	Depression, ASD	No
Cunningham et al., 2015, USA, (15)	Patients aged between 14-24 years treated at the ED following assault	Urban public ED, high crime rates in region	Assault, sexual assault and child abuse excluded	Depression, PTSD	Yes, DSM-IV
Elklit et al., 2003, Denmark, (26)	Patients aged 18 years and older who are victims of physical assault, treated at the ED	ED	Assault, mean Injury Severity Score 1.47, two-third of the sample had head and face injuries	ASD, PTSD	No
Fein et al., 2002, USA, (16)	Patients aged between 12-24 years treated at the ED for intentional violence	Urban EDs	Assault/fights, child abuse and domestic violence excluded	ASD, PTSD	No
Hunt et al.,	Injured trauma survivors aged 18 years	Two level I	Stabbing	PTSD	Yes,

2016, USA, (20)	and older, admitted to trauma center, 8.6% of the patients were victims of intentional stabbing	trauma centers			DSM-V
Johansen et al., 2006, Norway, (27)	Patients aged over 18, treated at the ED following assault	ED	Assault, domestic violence excluded	PTSD	No
Johansen et al., 2007, Norway, (28)	Patients aged 18 years and older, treated at the ED following physical assault	ED	Assault, domestic violence excluded	PTSD	No
Kleim et al., 2007, UK, (24)	Patients treated at the ED following assault, mean age 35 years	ED	Assault, domestic violence excluded	ASD, PTSD	PTSD only, DSM-IV
McCart et al., 2005, USA, (17)	Patients aged 9-18 years, treated at the ED following assault	ED	Assault, with and without weapons	Depression, PTSD	No
Pailler et al., 2007, USA, (18)	Patients aged between 12-17, treated at the ED following a violence-related event	ED	Violent event, child abuse excluded	Depression, ASD, PTSD	No
Purtle et al., 2014, USA, (19)	Patients aged between 7-17 years who sustained intentional interpersonal injury treated at the ED	Urban level I trauma center	Violent event, child abuse, domestic violence, and sexual assault excluded	PTSD	No
Roy-Byrne et al., 2004, USA, (22)	Patients aged 18 years and older, admitted to ED following sexual or	Urban level I trauma center	Sexual or physical assault	PTSD	Yes, DSM-IV

	physical assault, not requiring hospitalization				
Sullivan et al., 2017, USA, (21)	Patients aged 18 years and older, admitted to the trauma service for at least 24 hours following aggravated assault	Urban level I trauma center	Aggravated assault and gunshot wounds	Depression, PTSD	No
Walters et al., 2007, UK, (25)	Patients aged over 16 years, treated at the ED following assault	ED	Assault, no further exclusion criteria	PTSD	No

Abbreviations: ASD: acute stress disorder, ED: emergency department, PTSD: post-traumatic stress disorder.

[1] Are all DSM-IV or DSM-V diagnostic criteria for ASD, PTSD, or depression met, e.g. assessed by means of a structured clinical interview?

Table 2: Overview of PTSD, ASD, and depression prevalence rates and diagnostic instruments

PTSD (n=15)	Instrument, cut-off	No. / total no.	Prevalence in % (95% CI)				
			<1 month	1 month	3 months	6 months	12 months
Alarcon et al. (13)	PCL-C, ≥35	7/16	-	43.7 (11.4-76.2)	-	-	-
Bisson et al. (23)	TSQ, ≥6	338/3,349	59.1 (52.8-65.4)	-	-	-	-
Cunningham et al. (15)	MINI, DSM-IV criteria	30/184	-	-	-	-	16.3 (10.5-22.1)
Elklit et al. (26)	HTQ, ≥3 on all scales	26/118	-	-	-	22.0 (13.5-30.5)	-
Fein et al. (16)	CATS, ≥27	4/96	-	-	5.8 (0.12-11.5)	-	-
Hunt et al. (20)	CAPS, DSM-V criteria	7/12	-	58.3 (15.1-100)	-	-	-
Johansen et al. (27)	PTSS-10[1,2]	46/138	-	33.3 (23.7-43.0)[3]	-	-	-
Johansen et al. (28)	PTSS-10[1,2]	20/70, 17/70, 19-70	-	28.6 (16.0-41.1)	24.3 (12.7-35.8)	-	27.1 (14.9-39.3)
Kleim et al. (24)	SCID, DSM-IV criteria	49/205	-	-	-	23.9 (17.2-30.6)	-

McCart et al. (17)	TSCC, NR	7/89	7.1 (1.85-12.4)	-	-	-	-
Pailler et al. (18)	CATS, ≥27	3/158	-	-	-	1.9 (3.8-12.7)	-
Purtle et al. (19)	CTSQ, ≥5	31/47	66.0 (42.7-89.2)	-	-	-	-
Roy-Byrne et al. (22)	CAPS, DSM-V criteria	14/23, 7/23	-	60.9 (29.0-92.8)	30.4 (7.9-53.0)	-	-
Sullivan et al. (21)	PC-PTSD, ≥3	33/87	37.9 (25.0-50.9)	-	-	-	-
Walters et al. (25)	DTS[4]	NR	-	11 (NR)	-	7.7 (NR)	-

ASD (n=5)	**Instrument, cut-off**	**No. / total no.**	**Prevalence in % (95% CI)**		
			<1 week	1 week	>1 week
Boccelari et al. (14)	ASDS, >36	221/541	-	40.9 (35.5-46.2)	-
Elklit et al. (26)	HTQ, ≥2	47/196	24.0 (17.1-30.8)	-	-
Fein et al. (16)	ISRC[5]	17/69	24.6 (12.9-36.3)	-	-
Kleim et al. (24)	ASDS, NR	37/222	-	-	16.7 (11.3-22.0)

Pailler et al. (18)	ISRC, NR	46/394	-	11.7 (8.3-15.0)	-
Depression (n=5)	**Instrument, cut-off**	**No. / total no.**	**Prevalence in % (95% CI)**		
			<1 month	≥ 1 month	
Boccelari et al. (14)	PHQ, NR	191/541	35.3 (30.3-40.3)	-	
Cunningham et al. (15)	MINI, DSM-IV criteria	31/184	-	16.8 (10.9-22.8)	
McCart et al. (17)	TSCC, NR	5/89	5.1 (0.6-9.6)	-	
Pailler et al. (18)	CDI-SF, >65	12/394	3.0 (1.3-4.8)	-	
Sullivan et al. (21)	PHQ-8, ≥10	36/87	41.4 (27.9-54.9)	-	

Abbreviations: ASD: acute stress disorder, ASDS: Acute Stress Disorder Scale, CAPS: Clinician Administered PTSD Scale, CATS: Child and Adolescents Trauma Survey, CDI-SF: Children's Depression Inventory Short Form, CTSQ: Child Trauma Screening Questionnaire, DTS: Davidson Trauma Scale, HTQ: Harvard Trauma Questionnaire, ISRC: Immediate Stress Response Checklist, MINI: Mini International Neuropsychiatric Interview, NR: not reported, PC-PTSD: Primary Care PTSD, PCL-C: PTSD Checklist-Civilian, PHQ(-8): Patient Health Questionnaire (8), PTSD: post-traumatic stress disorder, PTSS-10: Post Traumatic Symptom Scale 10, SCID: Structured Clinical Interview for DSM-IV, TSCC: Trauma Symptom Checklist for Children, TSQ: Trauma Screening Questionnaire.

[1] Cut-off: a score of four or more on six or more items indicating PTSD.

[3] Males: 33/110 (30%), females: 13/28 (46%).

[2] IES-15 (Impact of Event Scale 15) was used as a secondary instrument, prevalence rates: 25.7% 1 month, 30.0% 3 months, 31.4% 12 months.

[4] Cut-off: at least one re-experiencing, three avoidance and two hyperarousal symptoms at a frequency of at least twice in the previous week.

[5] Cut-off: at least one significant symptom in every category.

Quality assessment

Of all 64 possible scoring options (four quality domains times sixteen studies), the reviewers disagreed on five scoring options resulting in a disagreement rate of 7.8%. Two of the disagreements belonged to the study participation domain and three to the outcome measurement domain. Disagreements were resolved after discussion. Table 3 describes the risk of bias per domain (study participation, study attrition, outcome measurement, and statistical analysis) for all studies included. The study by Pailler et al. (18) was the only study with a low risk of bias on all four domains. The study attrition domain was mainly scored as high risk (83%) because of low participation rates and/or poor descriptions of the patients lost to follow-up. One study scored 'low risk' in this domain (18). The statistical analyses and the presentation of the results were adequate in all studies. Therefore, all studies scored 'low risk' on the statistical analyses domain. The outcome measurement domain was mainly scored as low risk (67%). The majority had a low risk score for the study participation domain (67%), but one study had a high risk of bias because the recruitment process, inclusion criteria, and baseline characteristics were not reported adequately (26).

Table 3: QUIPS risk of bias assessment

Study	Study participation	Study attrition	Outcome measurement	Statistical analysis and presentation
Alarcon et al. (13)	Low	High	Low	Low
Bisson et al. (23)	Moderate	High	Low	NA
Boccelari et al. (14)	Moderate	High	Moderate	Low
Cunningham et al. (15)	Low	High	Moderate	Low
Elklit et al. (26)	High	High	Low	Low
Fein et al. (16)	Low	Moderate	Moderate	Low
Hunt et al. (20)	Low	Moderate	Low	Low
Johansen et al. (27)	Low	High	Moderate	Low
Johansen et al. (28)	Low	High	Moderate	Low
Kleim et al. (24)	Low	High	Low	Low

McCart et al. (17)	Moderate	High	Low	Low
Pailler et al. (18)	Low	Low	Low	Low
Purtle et al. (19)	Low	High	Low	Low
Roy-Byrne et al. (22)	Low	High	Low	Low
Sullivan et al. (21)	Low	High	Low	Low
Walters et al. (25)	Low	High	Low	Low

Abbreveations: NA: not applicable

Discussion

This systematic review provides an overview of the published literature reporting the prevalence rates and trajectories of PTSD, ASD, and depression following violence related injury treated at the ED or hospital. The quality of the included studies was assessed. We identified sixteen studies reporting the prevalence of ASD, PTSD, or depression. The reported prevalence rates were diverse across different follow-up points resulting in a wide range. The quality assessment indicated that almost all studies were susceptible to bias due to low response rates and loss to follow-up.

In a previous meta-analysis on the prevalence of PTSD among trauma-exposed children and adolescents, an overall pooled prevalence rate of 15.9% was reported (29). The pooled prevalence rate for victims of interpersonal violence was 25.2%. The time of diagnosis was not specified, however. We found prevalence rates ranging from 1.9% (3 months) to 66% (<1 month) among children and adolescents. It is not warranted to aggregate these prevalence rates given the differences in the timing of the diagnosis and diagnostic instruments. White et al. (30) reported a PTSD prevalence of 14.3% among an adult sample that experienced a traumatic event. Again, this finding is difficult to compare with our results as the PTSD prevalence ranged from 7.7% (6 months) to 60.9% (<1 month). Brewin et al. (31) reported an ASD prevalence estimate of 19% among adult violent crime victims who were not necessarily treated for injury. This prevalence rate is comparable with the ASD prevalence rates reported in four included studies (11.7-24.6%), but one study reported a prevalence rate of 41% (14). These findings suggest that ASD is highly prevalent in patients with violence related injury and that the prevalence is comparable to populations consisting of injured and non-injured violence victims.

Four studies reported PTSD prevalence rates before one month after the traumatic event (17, 19, 21, 23), which is not in accordance with the DSM (IV and V) criteria. It could be

possible that these PTSD symptoms resulted from other traumatic events. Data on pre-existing PTSD, ASD, and depression among the study samples were not available, however. Consequently, it is unclear whether mental disorders were already present prior to the injury. This limitation is common in violence and injury research, but has to be taken into account when interpreting the results. It is also possible that people who already have PTSD, ASD or depression are more likely to be involved in interpersonal violence. It is known that PTSD is associated with more risk behavior (32) which could increase the likelihood of involvement in violence. Information regarding the diagnostic status before the injury is therefore valuable for interpreting the prevalence rates.

All studies were conducted in high-income countries, of which the vast majority in the United States. The findings of this review are therefore limited to these countries. Healthcare systems in high-income countries are relatively well established, which facilitates recognition, prevention, and treatment. It is therefore likely that the prevalence rates and trajectories of PTSD, ASD, and depression are different in middle and low-income countries.

Strengths and limitations

One of the strengths of our study is that standard methods for conducting and reporting systematic reviews were followed (11). Furthermore, psychological, medical, and other relevant literature databases were searched exhaustively. Another strength is that we assessed the quality of the included studies. A limitation of our review is that the search was restricted to studies published in scientific peer-reviewed journals in English language. We did not consider dissertations, unpublished material or studies in non-English language, which could have biased our findings.

Recommendations

For future research, we recommend uniformity in diagnostic procedures. Structured diagnostic interviews by a clinician are preferred, but this is often not feasible. These interviews are time consuming and costly as they require involvement of trained professionals. Nevertheless, validated questionnaires can be used as an approximation. Our findings show that a large variety of questionnaires are available, however. Estimates of PTSD prevalence tend to vary according to the diagnostic criteria used, which underpins the need for uniformity in diagnostic procedures. These differences in diagnostic procedures could be reduced by establishing international guidelines on assessing mental health problems among trauma patients. Although international uniformity in diagnostic

procedures would increase the comparability of PTSD, ASD and depressions estimates, one should pay attention to ethnocultural differences. The validity of responses to measures may vary between populations, cultures, and countries (33). Values and norms associated with culture guide perception and individual responses, including psychiatric symptoms (34). Marshall et al. (35) investigated posttraumatic stress among a sample of Hispanic, non-Hispanic Caucasian, and African American survivors of physical injury. They found that the Hispanic group reported different symptoms and higher levels of overall posttraumatic distress. Such results raise questions regarding whether certain cultures truly experience higher levels of distress after experiencing a traumatic event, or whether cultural factors have an impact on the symptom manifestation only.

One of the sixteen included studies reported gender-specific prevalence rates. We recommend to report gender specific prevalence rates, since it is known that women are more likely to develop PTSD after trauma than men (29, 36). Trajectories of PTSD, ASD, and depression can be better understood when distinguishing gender specific prevalence rates.

Prevalence rates should also be reported separately for injury types, such as sexual versus physical assault injuries and injuries caused by strangers versus family. The studies in the current review included patients with different injury types but prevalence rates were not reported separately. Identifying injury types that are associated with higher rates of PTSD, ASD, or depressions may lead to earlier identification of high risk patients. Furthermore, ethnocultural differences in prevalence estimates should be considered in future studies. Cultural factors shape the subjective meaning of traumatic events, which in turn influences symptom expression (37).

Only few studies had follow-up measurements beyond one year after the violent incident. Previous studies suggest that the course of PTSD may vary over time. Prospective assessments are required to study the course of mental disorders following violence related injury treated at the ED or hospital. Since there are indications that the prevalence of PTSD among victims of intentional violence increases over time (5) it is relevant to know what the trajectories of PTSD and other mental disorders are for individuals who sustained injury following violence. For future research, extending the follow-up could contribute to better understanding of mental disorder trajectories following violence related injury.

Conclusions

Heterogeneity resulting from the use different diagnostic instruments limited comparability of the ASD, PTSD, and depression prevalence rates. The reported

prevalence rates should be interpreted carefully as almost all studies were susceptible to bias due to low response rates. Definitive or broad statements on the prevalence rates and trajectories are therefore not warranted. Study participation and loss to follow-up require more attention in future studies. Uniformity in diagnostic procedures is needed for future studies on mental disorders following violence related injury.

Appendices available at www.rhophuis.com

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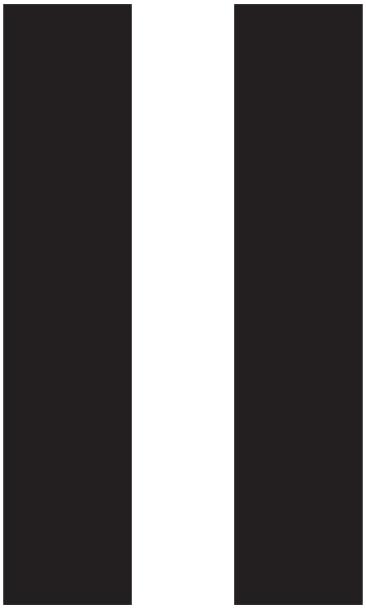

PART II

Cost-effectiveness modeling

CHAPTER 5

Early intervention for subthreshold panic disorder in the Netherlands: A model-based economic evaluation from a societal perspective

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Abstract

Background. Panic disorder (PD) is associated with impaired functioning and reduced quality of life. In the Netherlands, almost 2% of the population experiences clinically relevant panic symptoms without meeting the diagnostic criteria for PD, which is referred to as subthreshold PD (STHPD). Evidence suggests that subthreshold mental disorders may have a similar impact on quality of life and functioning in comparison with full-blown mental disorders, which draws attention to the need for interventions for STHPD. These interventions are currently not systematically provided in clinical practice. This study aims to investigate the population cost-effectiveness of adding a CBT-based early intervention for adults with STHPD to the existing healthcare for people with PD in the Netherlands.

Methods. A health-economic Markov model was constructed in order to compare quality adjusted life-years (QALYs) and societal costs of adding an early intervention to usual care for PD. The model compares usual care with an alternative program in which usual care is supplemented with a CBT-based early intervention. Input parameters for the model were derived from national sources and published literature where possible, and based on expert opinion otherwise. Probabilistic and deterministic sensitivity analyses were conducted to evaluate the uncertainty of the model input parameters.

Results. On average, the added CBT-based early intervention was dominant in comparison with usual care, meaning that the early intervention yields more QALYs at lower costs. At a willingness-to-pay threshold of €20,000 per QALY, the cost-effectiveness probability of the added early intervention was 98%. Sensitivity analyses showed that the results were robust.

Conclusions. This study showed that offering an early intervention in addition to usual care for PD is potentially cost-effective, but it should be further investigated to what extent trial results can be extrapolated to the level of the population before such interventions are implemented on a large scale.

Introduction

Panic disorder (PD) is a disabling anxiety disorder that is associated with impaired functioning and reduced quality of life (1, 2). Individuals with PD experience unexpected panic attacks characterized by symptoms such as hyperventilation, palpitations and derealisation (3). Important characteristics of PD are the avoidance of potential anxiety-provoking situations and the anticipated fear of having future panic attacks (3).

PD is associated with medically unexplained symptoms and high healthcare utilization (4, 5). On average, individuals who experience panic symptoms visit general practitioners, medical specialists, and emergency departments more often than the general population (6).

About 2% of the Dutch population experiences clinically relevant panic symptoms without meeting the diagnostic criteria of a full-blown PD diagnosis (7). This subclinical form of PD is generally referred to as subthreshold PD (STHPD) (8). In the Netherlands, STHPD is almost as prevalent as full-blown PD (1.9% versus 2.2%) (7).

As a result of the currently applied diagnostic thresholds for PD, many individuals with clinically relevant symptoms might not receive appropriate treatment (9), which could lead to progression of morbidity and deterioration of quality of life resulting in full-blown PD (10, 11). Studies have shown that subthreshold mental disorders may have a similar impact on quality of life and functioning on the level of the population in comparison with full-blown mental disorders due to a higher prevalence of subthreshold disorders (9, 11). Although the STHPD prevalence in the Netherlands is lower than the prevalence of PD, the health impact and costs of STHPD are substantial.

The societal per capita costs for PD and STHPD in the Netherlands are respectively €8,000-10,000 and €6,000 per year (7, 12). The indirect non-medical costs for PD and STHPD are both higher than the indirect non-medical costs for phobias, social anxiety disorder, and generalized anxiety disorder (12), which shows that that PD and STHPD are both associated with substantial productivity losses. The relatively high prevalence rate and societal costs of STHPD emphasize that there is a treatment need.

Various psychological and pharmacological interventions for PD have been shown to be effective and cost-effective (13-15), but the evidence on the effectiveness and cost-effectiveness of interventions for treating STHPD is less substantial. Meulenbeek et al. (16) showed that a cognitive behavioral therapy (CBT) based early intervention for adults with STHPD significantly reduced panic symptoms. This intervention called 'Don't Panic' is group-based. An economic evaluation of this intervention resulted in an incremental cost-

effectiveness ratio (ICER) of €6,000 per PD-free survival gained when compared to usual care (17).

Although these studies (16, 17) show promising results in terms of effectiveness, early interventions for treating STHPD are currently not systematically offered in Dutch clinical practice. Before such interventions can be implemented in clinical practice, further evidence on the cost-effectiveness at the population level is essential for policy makers. A health-economic model can contribute to such evidence. Therefore, this study aims to investigate the population cost-effectiveness of adding a CBT-based early intervention for adults with STHPD to the existing healthcare for people with PD in the Netherlands by means of a health-economic Markov model.

Methods

The methods and reporting of this model-based economic evaluation are in concordance with the Consolidated Health Economic Evaluation Reporting Standards (CHEERS) statement and ISPOR recommendations (18, 19). A completed CHEERS checklist has been added to appendix 4.1.

Study population and epidemiology

The study population in the model comprised the Dutch adult population aged 18-65 years (20, 21). Prevalence and incidence estimates of PD and STHPD were obtained from the Netherlands Mental Health Survey and Incidence Study, a cohort study on the epidemiology of mental disorders in the Dutch general population (22). The annual prevalence rates of PD and STHPD were respectively 2.2% (95%CI 1.9–2.6) and 1.9% (95%CI 1.6–2.2) (9). DSM-III-R diagnostic criteria for PD were applied. STHPD was defined as having at least one experience of panic during the last year in a situation in which the panic attack is not considered normal (9). This experience must have been accompanied by at least four of the thirteen panic symptoms according to the DSM-III-R, and may not be of organic cause.

The annual incidence of PD in the Netherlands was 0.52% (95%CI 0.37-0.73) (23). Within two years, 43.3% of the PD patients and 23.8% of the STHPD patients had chronic panic complaints, whereas respectively 21.4% and 37% of the STHPD patients who reached remission had a recurrence (24).

Usual care

The usual care scenario (Table 1) reflects usual care for PD in the Netherlands. We assumed that the recommended interventions as described in Dutch multidisciplinary treatment guideline for anxiety disorders (25) represent current clinical practice.

Recommended psychological interventions for PD are therapist-led interventions based on cognitive or behavioral therapy (25). In Dutch clinical practice, these interventions are generally offered combined as CBT. Therefore, CBT was considered as psychological intervention in the model. We defined CBT as a psychological intervention based on learning theory and cognitive restructuring (26).

Selective serotonin inhibitors (SSRIs) are first-choice pharmacotherapy for PD and tricyclic antidepressants (TCAs) are second-choice pharmacotherapy (25). Both SSRIs and TCAs were added to the model as pharmacological interventions. SSRIs are first-choice pharmacotherapy as they are generally better tolerated and cause fewer adverse events in comparison with TCAs (25).

Furthermore, combination therapy consisting of pharmacological treatment and CBT was added to the model. Benzodiazepines were not considered because they are only recommended for acute and situation-specific treatment (25).

Table 1: Base-case and alternative scenario

Intervention	Uptake usual care (%)	Uptake additional CBT-based early intervention (%)	Adherence (%)
PD			
CBT	8.8	8.8	70
SSRI	9.2	9.2	57
TCA	2.4	2.4	49
Combination therapy	9.0	9.0	70
STHPD			
CBT-based early intervention	0	10	70

Additional CBT-based early intervention

In order to investigate the additional effect of adding an early intervention for STHPD to the current clinical practice for PD in the Netherlands, usual care was supplemented with an early intervention for treating STHPD (Table 1).

The early intervention in the model was based on the ‘Don’t Panic’ intervention described

by Meulenbeek et al. (16) and Smit et al. (17). The early intervention is a CBT-based group course for adults aged eighteen years and older (6-12 participants) with STHPD. The group course consists of eight weekly sessions of two hours guided by a prevention worker and a mental health clinician. The group course covers psycho-education, lifestyle advice, stress coping, cognitive restructuring, in vivo exposure, and a relapse prevention training.

Intervention uptake and adherence

In the Netherlands, 29.4% of the PD patients utilize mental healthcare (27). As it is not known how often specific interventions for PD are offered, we used Australian data regarding mental healthcare utilization as an approximation (28). Based on expert opinion, respectively 85% and 15% of the Dutch PD patients receiving pharmacotherapy use SSRIs and TCAs, of which one third receives combination therapy (both pharmacotherapy and CBT) due to unsuccessful treatment outcomes. Because early interventions are currently not offered systematically in the Netherlands, the uptake in usual care is set at 0%. In the scenario with the added CBT-based early intervention, the uptake rate for the early intervention is set at 10%. For the remaining interventions, we applied equal uptake rates. We applied an adherence rate of 70% for all interventions considered in the model, assuming that the effectiveness of interventions in clinical practice is generally lower than in clinical trials. Additionally, we applied drop-out rates for SSRI and TCA treatment (respectively 18% and 30%) based on the Dutch multidisciplinary guideline for anxiety disorders (25), resulting in lower adherence rates. We conservatively assumed that non-adherent patients had no utility gain (no effect of treatment). Full intervention costs were incurred for non-adherent patients. Table 1 describes the uptake and adherence rates for usual care and the early intervention scenario.

Structural assumptions

A four-state Markov model was constructed using Microsoft Excel 2013 in order to assess the incremental costs and quality adjusted life-years (QALYs) of the added CBT-based early intervention versus usual care. The model structure, as depicted in Figure 1, is based on the availability of epidemiological and clinical evidence. The cycle length was one year, corresponding to the available epidemiological evidence, which generally reports annual transition rates. Subjects either remain in the same health state or switch to a connecting health state, assuming that only one switch per cycle is possible. We applied a time horizon of five years.

Four mutually exclusive health states were considered in the model; panic-free (PF),

STHPD, PD, and death. Individuals who neither met the earlier mentioned diagnostic criteria for PD and STHPD were in the PF health state. We assumed that STHPD was intermediate between PF and PD, meaning that individuals with PD can only reach the PF state by crossing the STHPD health state and vice versa. This assumption implies that the incidence of PD solely occurs from STHPD.

Model parameters

Health state utilities. The effectiveness of the interventions was expressed in QALYs, which required the use of utility scores of the included health states. A utility score reflects health-related quality of life ranging from 0 (death) to 1 (full health). Utility values can be multiplied by their duration in years to calculate QALYs. One QALY gained reflects one extra life-year in full health gained. For the individuals who were not diagnosed with (STH)PD, we used a published utility score of the Dutch general population (29). Utility data for the PD health state were derived from the European Study of the Epidemiology of Mental Disorders (30). The utility score for the STHPD health state was derived from a Dutch disability weight study (31). All utility scores were based on the EQ-5D. STHPD and PD utilities were multiplied with the general population utility in order to ensure that improvements from STHPD and PD to PF reflected utility gains as expected by burden of disease studies (30, 31). This adjustment was deemed necessary to improve the comparability of health state utility values taken from different sources. In a sensitivity analysis, we investigate the impact of this correction. The health state utilities are reported in Table 2, alongside with the other parameter values.

Health gains. Interventions aim to increase utility and thereby QALYs. In the model, QALY gains due to interventions aimed at treating PD were based on effect sizes from a recent meta-analysis on interventions for anxiety disorders (14). The effect size of the early intervention was based on trial data (16). Effect sizes were converted to utility gains by means of a conversion method described by Sanderson et al (32). The effect sizes and conversion values are presented in appendix 4.2. The preventive effect of the early intervention on progression from STHPD to PD, expressed as a decrease in the transition rate from SHPD to PD, was based on the study by Meulenbeek et al. (16).

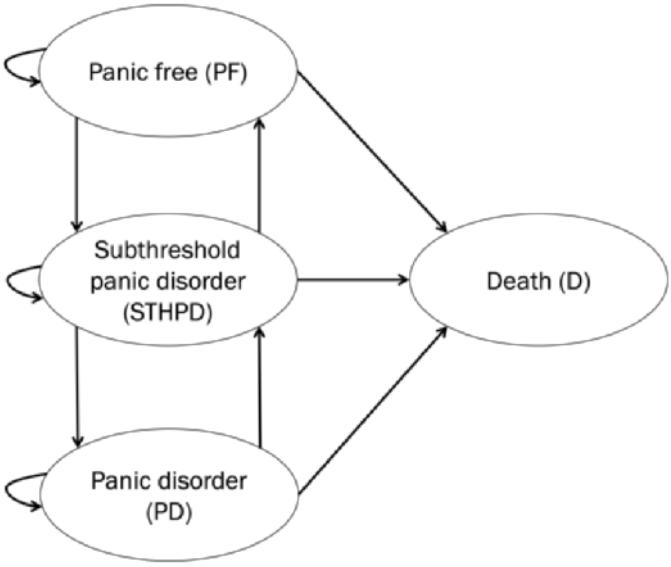

Figure 1: Markov model structure

Transition probabilities. Transition probabilities in terms of incidence, recurrence, and chronicity as described earlier reflect usual care since they were based on cohort studies in which participants had no restrictions in terms of healthcare resources. Ideally, intervention specific transition probabilities are included in the model. We used intervention specific probabilities for the early intervention, but not for the remaining interventions due to a limited availability of evidence.

Resource use and cost data. Direct medical costs, direct non-medical costs, and indirect non-medical costs for the PD and STHPD health states were derived from a cost-of-illness study by Batelaan et al (7). The authors were contacted for a detailed overview of the cost categories. Direct medical costs relate directly to medical care, such as doctor visits. Direct non-medical costs are out-of-pocket costs, for example travel costs due to doctor visits. Indirect non-medical costs consist of costs due to productivity losses. We calculated the societal costs by summing up the direct medical costs, direct non-medical costs, and indirect non-medical costs. All costs are expressed in euros (€) for the reference-year 2014. We used the Dutch price index (Central Bureau of Statistics, the Netherlands) in order to express costs in 2014 euros

Intervention specific costs. Unit cost prices were obtained from the Dutch Guideline for Health Economic Evaluations (33). Costs for medication were based on Dutch

reimbursement rates (34). The intervention-specific resource use is described in Table 2. The costs for the early intervention were derived from the economic evaluation of the 'Don't panic' intervention by Smit et al. (17). The intervention costs were €905 per patient (indexed for the year 2014). The intervention consists of eight CBT sessions of two hours each by a prevention worker and a clinician, followed by one booster session three months after completion.

Cost-effectiveness analysis. Mean costs and QALYs were estimated for usual care and the added CBT-based early intervention. Both costs and effects were discounted annually. The incremental cost-effectiveness ratio (ICER) was calculated by dividing the difference in costs between both scenarios by the difference in QALYs. The ICER represents the cost of an additional life-year in full health gained. A cost-effectiveness acceptability curve was plotted, which shows the probability that the added early intervention is cost-effective for different willingness-to-pay (WTP) thresholds. The early intervention was deemed cost-effective when the ICER is below the WTP-threshold of €20,000 per QALY, a threshold for disorders with disability weights between 0.1 and 0.4 according to the Dutch Healthcare Institute recommendations (35).

Handling uncertainty

A probabilistic sensitivity analysis was performed in order to take into account the uncertainty surrounding the point estimates of the input parameters. Probability distributions were assigned to the parameters, after which 10,000 iterations were performed by drawing random values for the input parameters. Utility parameters were assigned a normal distribution, and cost parameters were assigned a gamma-distribution as presented in Table 2. The mean incremental costs and QALYs were calculated by averaging the 10,000 iterations.

Deterministic sensitivity analyses explored the impact of making several assumptions: applying different uptake rates for the interventions, varying the effectiveness of the early intervention, the use of alternative time horizons of one and ten years, and the use of utility values that were not corrected for the baseline level of the general population.

Table 2: Model input parameters

Input parameter	Deterministic value	Probabilistic distribution	Source
Discount rate costs	4%	Fixed	Dutch Guideline for Health Economic Evaluations (33)
Discount rate outcomes	1.5%	Fixed	Dutch Guideline for Health Economic Evaluations (33)
Indirect non-medical costs per health state (annual)			
PF	€6,643	Gamma	Based on data by Batelaan et al. (7) and Smit et al. (12)
STHPD	€9,741	Gamma	Based on data by Batelaan et al. (7)
PD	€16,771	Gamma	Based on data by Batelaan et al. (7)
Direct medical costs (annual)			
PF	€340	Gamma	Based on data by Batelaan et al. (7)
STHPD	€1,503	Gamma	Based on data by Batelaan et al. (7)
PD	€666	Gamma	Based on data by Batelaan et al. (7)
Direct non-medical costs (annual)			
PF	€99	Gamma	Based on data by Batelaan et al. (7)
STHPD	€494	Gamma	Based on data by Batelaan et al. (7)
PD	€858	Gamma	Based on data by Batelaan et al. (7)
Health state utilities			
PF	0.869	Normal, SE: 0.0054	Versteegh et al. (29)
STHPD	0.730	Normal, SE: 0.037	Based on Versteegh et al. (29) and Stouthard et al. (31)
PD	0.660	Normal, SE:	Based on Versteegh et al. (29)

		0.030	and Kaltenthaler et al. (30)
Transition probabilities			
PF to STHPD	0.0016	Fixed	Calculations based on epidemiology (7, 24)
STHPD to PF	0.0815	Fixed	Calculations based on epidemiology (7, 24)
STHPD to PD	0.6037	Fixed	Calculations based on epidemiology (7, 24)
STHPD to PD transition is lowered by the early intervention, based on a RR of 0.538			Meulenbeek et al. (16)
PD to STHPD	0.5214	Fixed	Calculations based on epidemiology (7, 24)
Any state to 'Death'	0.0028	Fixed	Based on Dutch national statistics, averaged for the population aged 18-65 years (36)
Utility gain after intervention			
CBT	0.0327	Normal	Based on Sanderson et al. (32) and Bandelow et al. (14)
SSRI	0.0450	Normal	Based on Sanderson et al. (32) and Bandelow et al. (14)
TCA	0.0445	Normal	Based on Sanderson et al. (32) and Bandelow et al. (14)
Combination therapy	0.0568	Normal	Based on Sanderson et al. (32) and Bandelow et al. (14)
Early intervention	0.0655	Normal	Based on Sanderson et al. (32) and Meulenbeek et al. (16)
Intervention costs (per person)			
CBT [1]	€1,176	Gamma	Dutch Guideline for Health Economic Evaluations (33), Expert opinion
SSRI [2]	€1,128	Gamma	Dutch Guideline for Health Economic Evaluations (33), Expert opinion

TCA [3]	€1,200	Gamma	Dutch Guideline for Health Economic Evaluations (33), Expert opinion
Combination therapy [4]	€2,315	Gamma	Dutch Guideline for Health Economic Evaluations (33), Expert opinion
Early intervention [5]	€905	Gamma	Smit et al. (17)

[1] 12 sessions in Basic mental healthcare.
[2] Defined Daily Dose for one year (average SSRI costs) plus 9.5 sessions (min. 8 and max. 12) in specialized mental healthcare.
[3] Defined Daily Dose for one year (average TCA costs) plus 9.5 session in specialized mental health care.
[4] 12 general mental health institution sessions, Defined Daily Dose for one year (average TCA/SSRI costs) plus 9.5 sessions in specialized mental healthcare.
[5] Based on Smit et al. (17) (explained in the methods section).

Results

Over a period of five years, usual care resulted in 3.28 QALYs (95% CI 3.01-3.48) and €59,634 (95% CI 45,097-76,084) per patient on average, whereas the added CBT-based early intervention resulted in 3.30 QALYs (95% CI 3.10-3.49) and €59,355 (95% CI 44,984-75,621) per patient. All patients with STHPD and PD were included, regardless of whether they received any intervention. When only the STHPD patients are considered, usual care resulted in 3.47 QALYs (95%CI 3.16-3.77) and €43,099 (95%CI 28,402-60,779) on average per STHPD patient, and the added early intervention 3.58 QALYs (95%CI 3.27-3.89) and €44,512 (95%CI 29,448-62,668).

When both STHPD and PD patients are considered, the ICER equaled €-23,127 (95% CI -395,731-3,682) per QALY gained, meaning that the added early intervention resulted in more QALYs at lower costs on average in comparison with usual care. Figure 2 presents the cost-effectiveness plane, in which the ICERs for the 10,000 iterations are depicted. The majority of the ICERs were located in the lower-right quadrant of the incremental cost-effectiveness plane, indicating dominance.

Figure 3 shows the cost-effectiveness acceptability curve, in which the probability that the added early intervention is cost-effective in comparison with usual care is shown for a range of WTP threshold values. When society is willing to pay €20,000 per QALY, the cost-effectiveness probability of the added CBT-based early intervention is 98%.

Multiple one-way sensitivity analyses were performed in order to assess the robustness of the results. Table 3 reports the ICERs after altering different key parameters. All ICERs resulted on average in more QALYs at lower costs, indicating that the addition of the CBT-based early intervention is cost-saving on average. The confidence intervals of the reference case and sensitivity analyses ICERs indicate that there is a minimal chance that the added intervention will result in higher costs compared to usual care. However, these upper limits are far below the WTP threshold of €20,000 per QALY gained.

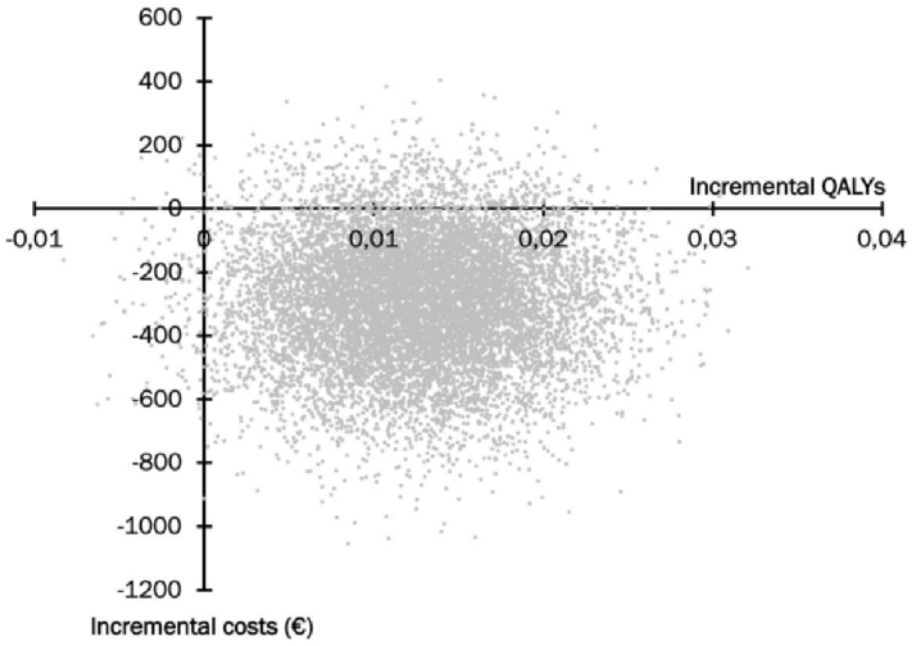

Figure 2: Incremental cost-effectiveness plane of the additional CBT-based early intervention versus usual care

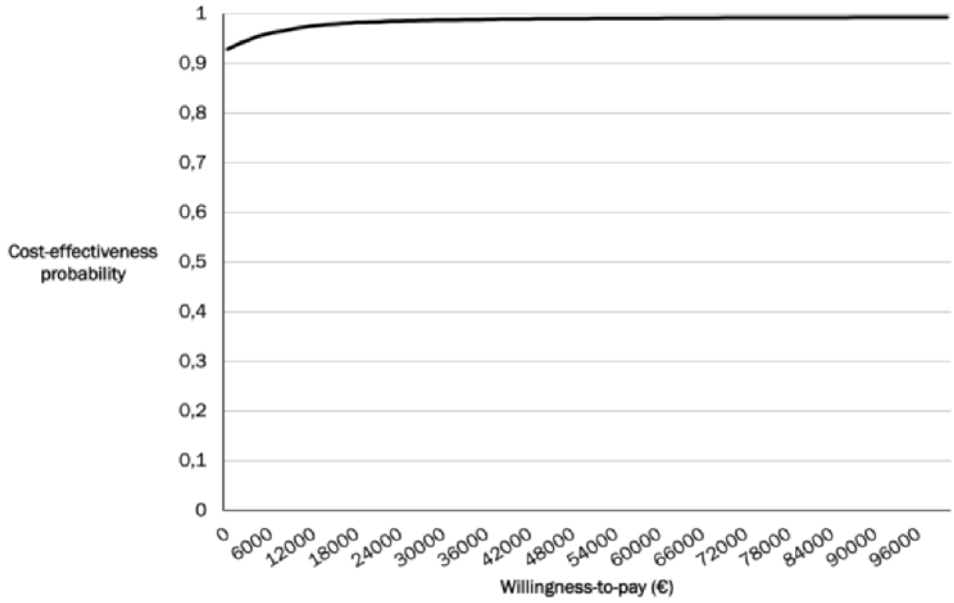

Figure 3: Cost-effectiveness acceptability curve

Table 3: Results of the one-way sensitivity analyses

	ICER	**95% CI**	
	Mean (€)	*2.5%*	*97.5%*
Reference case	-23,127	-395,731	3,682
Assumptions			
Time horizon 1 year	-14,529	-88,655	5,276
Time horizon 10 years	-58,531	-165,535	-318
Early intervention 5% uptake rate	-23,214	-372,735	3,521
Early intervention 15% uptake rate	-23,113	-335,890	3,366
Early intervention transition from STHPD to PD 10% lower	-18,507	-246,637	4,467
Early intervention transition from STHPD to PD 10% higher	-28,351	-657,641	2,654
Uptake rate PD interventions 100%	-20,706	-264,899	4,017
Uncorrected utility values	-22,894	-314,488	3,593

Discussion

Main findings

This study aimed to investigate the population cost-effectiveness of adding a CBT-based early intervention for adults with STHPD to the existing healthcare for people with PD in the Netherlands by means of a health-economic Markov model. Our main finding was that the added early intervention for STHPD with 10% uptake yields more QALYs at lower costs on average in comparison with usual care. When a WTP-threshold of €20,000 per QALY gained is assumed, the cost-effectiveness probability of the added early intervention is 98%. Multiple one-way sensitivity analyses supported this conclusion. Therefore, adding an early intervention to the currently available interventions for PD potentially makes the care for (STH)PD in the Netherlands more cost-effective from a societal perspective.

Comparison with other published studies in the field

Earlier, the cost-effectiveness of an early intervention in comparison with usual care was investigated alongside a trial (17). Although this intervention was cost-effective compared to usual care, the cost-effectiveness of adding the intervention to usual care for PD at the level of the population was not assessed. Furthermore, the time horizon of a trial-based economic evaluations is relatively short. In the current study, the evidence on early interventions for STHPD was extrapolated to the population level with an extended time horizon of five years.

A comparable study in the field of mental health reported that an early intervention for patients at high risk for psychosis was also cost-saving in comparison with care as usual (37). Our findings also suggest that offering an early intervention for STHPD has the potential to be cost-saving. Since the current evidence base on the cost-effectiveness of early interventions for STHPD is limited, more economic evaluations are needed to investigate the added value of such interventions.

Strengths and limitations

The current study adds evidence on the cost-effectiveness of treating STHPD on the level of the population. To our knowledge, this is the first health-economic model analyzing the cost-effectiveness of adding an early intervention for STHPD to usual care for PD in the Netherlands. Available evidence regarding epidemiology, clinical effectiveness, and costs was combined to support decision-making regarding the healthcare system for (STH)PD. The model was designed to reflect clinical practice as closely as possible by taking into

account uptake rates and adherence rates. These rates can be altered manually in the model in order to compare different scenarios.

Our study has several limitations. Ideally, model parameters are based on data reported in meta-analyses rather than single trials. Because the current evidence base on the effectiveness of early interventions for STHPD is limited, we derived effectiveness data for the early intervention from a single RCT with a sample size of 217 (16). Although the reported preventive effect of the early intervention on the full-blown PD diagnostic status was significant, the effectiveness of the CBT-based group intervention was investigated in one trial only. Further studies assessing the effectiveness of CBT-based early interventions are needed to confirm our preliminary results.

Intervention-specific transitions were not applied for interventions for PD in the model due to a lack of available evidence. This resulted in the assumption that patients who received interventions for full-blown PD had the same chance of remission as patients who did not receive treatment. Hence, the effect of the interventions for PD might have been underestimated. However, the utility was increased as a result of receiving an intervention, which yielded QALY gains for patients who received an intervention.

Comorbid conditions were not considered in the model, which we consider as a limitation. For instance, it is known that panic is frequently comorbid with other anxiety disorders, depression, and alcohol abuse (38, 39), which could lead to higher costs and lower quality of life. The costs input parameters were corrected for comorbid mental disorders, meaning that only the costs that can be attributed to (STH)PD were considered (7, 12). Consequently, the model does not take into account the possible effects of comorbid mental disorders on QALYs and costs. Comorbid conditions might increase societal costs and lower quality of life for individuals with (STH)PD, but it is unclear whether the effectiveness of the early intervention for STHPD is influenced by comorbid conditions.

Economic evaluations aim to identify the cost-effectiveness of interventions in order to improve efficiency in healthcare systems. It should be noted that other factors should also be taken into account in order to improve healthcare systems, such as patient preferences, feasibility, and medical ethics (40). However, the scope of this manuscript is restricted to the cost-effectiveness perspective.

Recommendations

Because our findings suggest that adding a CBT-based early intervention for STHPD is potentially cost-saving, policy makers should consider investing in the implementation of such interventions. However, further high-quality research is needed on the comparative

long-term outcomes of early interventions as well as on costs and transition probabilities associated with STHPD and PD in order to establish the relative cost-effectiveness of early interventions for STHPD with greater certainty. Based on the study data of Smit et al. (12), the direct medical costs for individuals with STHPD were higher than the direct medical costs for individuals with PD. Although these findings are based on a nationally representative study sample, further studies are needed to support this finding. Finally, it should be emphasized that health-economic modeling requires empirical validation. It is thus recommended that future studies on early interventions for STHPD test the findings generated by the current model.

Conclusions

This study showed that offering an early intervention in addition to usual care for PD in the Netherlands is potentially cost-saving. More research is needed on the comparative long-term outcomes of early interventions as well as on costs and transition probabilities associated with STHPD and PD in order to establish the relative cost-effectiveness of early interventions for STHPD with greater certainty.

Appendices available at www.rhophuis.com

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CHAPTER 6

Value of information analysis of an early intervention for subthreshold panic disorder: Healthcare versus societal perspective

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Abstract

Background. Panic disorder is associated with high productivity costs. These costs, which should be included in cost-effectiveness analyses (CEA) from a societal perspective, have a considerable impact on cost-effectiveness estimates. However, they are often omitted in published CEAs. It is therefore uncertain whether choosing a societal perspective changes priority setting in future research as compared to a healthcare perspective.

Objectives. To identify research priorities regarding the cost-effectiveness of an early intervention for subthreshold panic disorder using value of information (VOI) analysis and to investigate to what extent priority setting depends on the perspective.

Methods. We calculated the cost-effectiveness of an early intervention for panic disorder from a healthcare perspective and a societal perspective. We performed a VOI analysis, which estimates the expected value of eliminating the uncertainty surrounding cost-effectiveness estimates, for both perspectives.

Results. From a healthcare perspective the early intervention was more effective at higher costs compared to usual care (€17,144 per QALY), whereas it was cost-saving from a societal perspective. Additional research to eliminate parameter uncertainty was valued at €129.7 million from a healthcare perspective and €29.5 million from a societal perspective. Additional research on the early intervention utility gain was most valuable from a healthcare perspective, whereas from a societal perspective additional research would generate little added value.

Conclusions. Priority setting for future research differed substantially according to the perspective. Our study underlines that the health-economic perspective of CEAs on interventions for panic disorder must be chosen carefully in order to avoid inappropriate choices in research priorities.

Introduction

The results of model-based cost-effectiveness analyses (CEAs) are surrounded by uncertainty as the available information about costs and effectiveness of interventions in healthcare is rarely perfect (1). This uncertainty makes it difficult to guide policy makers because there is a risk of reimbursing suboptimal treatment options (2, 3). The increasing financial pressure on healthcare systems emphasizes that decision uncertainty should be minimized.

Reimbursement decisions based on CEAs require a willingness-to-pay (WTP) threshold, which represents the maximum amount society is willing to pay for health gains. In cost-effectiveness research, health gains are preferably expressed in quality adjusted life-years (QALYs) as QALYs allow for comparison between health conditions due the generic character of this outcome measure. When a WTP threshold for a QALY is determined, the net monetary benefit (NMB) of the treatment alternatives of interest can be calculated by multiplying the WTP by the QALYs gained and subtracting the additional costs. The treatment alternative with the highest expected NMB is the preferred option.

A value of information (VOI) analysis estimates the expected value of eliminating the uncertainty surrounding cost-effectiveness estimates (1, 4). This uncertainty can be minimized by performing additional research. Interventions might not be reimbursed because there is too much uncertainty about the right choice to be made. In that case, a VOI analysis can assist policy makers in deciding whether it is worthwhile to invest in additional research that could contribute to the reduction of this uncertainty. VOI also informs which specific model parameters might benefit the most from additional research (1, 2). For example, this additional research can pertain to healthcare costs, productivity costs, or treatment effectiveness.

The costs outside the healthcare sector are substantial among patients with mental disorders (5-8). In the Netherlands, these costs are higher than the healthcare costs for panic disorder as almost 90% of the societal costs is estimated to consist of productivity costs (9). A CEA performed from a societal perspective includes both healthcare costs and costs outside the healthcare sector. According to guidelines CEAs should be performed from a societal perspective in most countries (10), including the Netherlands (11), but many of these studies on panic disorder are performed from a healthcare perspective (12). Although one could expect that the cost-effectiveness of interventions for panic disorder would improve when including costs outside healthcare, only few studies support this assumption. More important, the role of the societal perspective in setting future

research priorities remains uncertain. Because CEAs from a societal perspective include additional parameters on costs outside healthcare, the research priorities identified by the VOI from a societal perspective might differ from the research priorities as identified by the analysis from a healthcare perspective.

In a previously published paper (13), we constructed a health-economic model to assess the cost-effectiveness of adding a cognitive behavioral therapy (CBT) based early intervention for adults with subthreshold panic disorder (STHPD) to the existing healthcare (usual care) for people with panic disorder in the Netherlands. We adopted a societal perspective as the model included both healthcare costs and productivity costs. When the costs outside healthcare are less relevant for a decision maker, a VOI analysis applied to a CEA from a societal perspective may identify inappropriate research priorities. This applies to panic disorder in particular because the productivity costs have a substantial impact on cost-effectiveness estimates (13).

To our knowledge, a VOI analysis applied to CEAs of interventions for (subthreshold) panic disorder has not yet been published. It therefore remains unclear whether additional research into specific model parameters to reduce uncertainty has additional value, and it also remains unclear whether these research priorities depend on the perspective that is applied. This information is valuable because decision makers not only have to decide which treatment alternative to adopt, but also whether more research regarding the decision is desirable (4). Moreover, the new Dutch guidelines for health-economic evaluations require quantification of uncertainty by means of VOI analysis (11). In this study, we therefore aim to identify research priorities regarding the cost-effectiveness of a CBT-based early intervention for STHPD using VOI analysis and to investigate to what extent priority setting depends on the perspective.

Methods

Cost-effectiveness model

The VOI analysis was applied to a previously developed model-based CEA. Based on this Markov model constructed in Microsoft Excel (13), we analyzed the cost-effectiveness of adding a CBT-based early intervention for adults with STHPD to the existing healthcare for people with panic disorder in the Netherlands. In brief, the modelled population was classified into three health states based on the presence and severity of panic symptoms: panic free, STHPD, and panic disorder. Death was added as an absorbing health state. Patients with STHPD experience clinically relevant panic symptoms, but they do not meet

the established diagnostic criteria for panic disorder (14). In the Netherlands, the prevalence of STHPD is comparable to the prevalence of panic disorder (1.9% versus 2.2%) (15).

We applied a cycle length of one year, meaning that patients remained in the same health state or switched to a connecting health state after one year. The time horizon of the analysis was five years. Because the long-term effect of the CBT-based early intervention is unknown we decided that applying the six months treatment effect to a CEA with a time horizon of >5 years would be inappropriate. In the previous cost-effectiveness study (13), a scenario analysis with a ten-year time horizon was tested. The results were comparable to the results based on a time horizon of five years. QALYs and costs of the intervention and usual care scenarios were the outcome of the model. We expressed monetary outcomes in euros (€) for the 2018 price level. More information on the model and its structure and underlying assumptions are published elsewhere (13). We assigned distributions to the model parameters in order to include the uncertainty surrounding them. In line with Briggs (2005) (16), cost parameters were assigned a gamma distribution, and utility parameters were assigned a beta distribution. A simulation of 10,000 model iterations was performed by drawing random values for the input parameters, which were used to estimate the mean incremental cost-effectiveness. The model parameters, 95% confidence intervals, probabilistic distributions, and sources are reported in the online supplementary files (5.1). The previously developed model was used as a basis for the current analyses (13), but several aspects were adjusted. Costs were uprated to a more recent price level (2018), utility data were assigned a beta distribution, and the early intervention relative risk that was multiplied with the STHPD to panic disorder transition probability was included in the probabilistic sensitivity analysis (log-normal distribution).

Treatment options

Usual care consists of the currently available care for panic disorder in the Netherlands covering psychotherapy, pharmacotherapy, or a combination of these therapies (13). We investigated the effect of adding a CBT-based early intervention for STHPD to the usual care for panic disorder in the Netherlands. The early intervention called ‘Don’t Panic’ is a group-based course for 6-12 adults covering CBT aspects such cognitive restructuring and in vivo exposure (17, 18). The intervention consists of eight weekly sessions guided by a prevention worker and mental health clinician. More detailed information about the treatment alternatives, adherence rates, and panic disorder intervention coverage rates

is published elsewhere (13).

Cost-effectiveness analysis

In addition to the previously published CEA from a societal perspective (13), we also calculated the cost-effectiveness from a healthcare perspective by excluding the productivity costs. The societal perspective often refers to the addition of merely productivity costs, while other non-healthcare costs could be relevant as well (19). In this research paper, however, the term societal perspective refers to the inclusion of healthcare costs and productivity costs. Therefore, the difference between the analyses from both perspectives solely consists of the inclusion of productivity costs. Mean costs and QALYs were estimated for usual care and the CBT-based early intervention. We applied annual discount rates for both costs (4%) and effects (1.5%) as recommended by the Dutch health-economic guidelines (13, 20). The incremental cost-effectiveness ratio (ICER) was calculated by dividing the difference in healthcare and societal costs between both scenarios by the difference in QALYs. We constructed a cost-effectiveness acceptability curve, which shows the cost-effectiveness probability of the usual care and early intervention scenarios for a range of WTP threshold values. The early intervention was deemed cost-effective when the ICER was lower than the WTP of €20,000 per QALY. The WTP threshold of €20,000 per QALY is a recommended threshold in the Netherlands for diseases with a relatively low disability weight (21).

VOI analysis

In the VOI analysis, the parameter uncertainty in the model was valued. Our VOI analyses consist of two parts: the expected value of perfect information (EVPI), and the expected value of partial perfect information (EVPPI). The EVPI represents the estimated value of eliminating the uncertainty in the model. More specific, the EVPI places an upper boundary on the costs of performing additional research to eliminate the uncertainty. It can thus be interpreted as the maximum of costs society should be willing to pay for additional evidence that eliminates the current decision uncertainty. Having perfect information regarding the cost-effectiveness of adding a CBT-based early intervention to usual care for panic disorder would protect against making suboptimal decisions regarding reimbursement and implementation as the cost-effectiveness estimate based on the model would be certain. The EVPI informs policy makers whether it is worthwhile to invest in further research that will contribute to the reduction of the current decision uncertainty. In the first step, the NMB for every model iteration of each treatment alternative (the

additional CBT-based early intervention and usual care) was calculated by multiplying the WTP by the QALYs and subtracting the costs. Thereafter we identified the preferred treatment alternative, which is the alternative that maximizes the NMB for the given WTP threshold based on current information in the model. Thereafter, the NMB when having perfect information (the EVPI) was calculated. Within each simulation run, the individual EVPI was equal to the difference between the NMB of the optimal treatment alternative based on the current information and the potential maximum NMB. The individual EVPI thus equals zero when the recommended option by the model under current uncertainty has the highest NMB. The individual EVPI was averaged over all 10,000 model runs. This method is illustrated in Table 1 for the analysis from a healthcare perspective. The same methods were applied to the analyses from a societal perspective.

Table 1: Calculating the individual Expected Value of Perfect Information (EVPI), example for the analysis from a healthcare perspective

	NMB [1]			
Model runs	CBT-based early intervention	Usual care	Maximum NMB	Net benefit gained when having perfect information
1	63,193	65,163	65,163	65,163-63,193=1,970
2	56,206	56,904	56,904	56,904-56,206=698
3	62,997	61,630	62,997	62,997-62,997=0
4	63,466	62,504	63,466	63,466-63,466=0
5	62,230	61,703	62,230	62,230-62,230=0
…	…	…	…	…
10,000	59,159	59,770	59,770	59,770-59,159=611
Mean [2]	60,831	60,643	61,483	61,483-60,831=652 [3]

Abbreviations: EVPI: expected value of perfect information, NMB: net monetary benefit.
[1] NMB was calculated by multiplying QALYs by the WTP threshold of €20,000 per QALY and subtracting costs. The early intervention resulted in the highest overall NMB for both perspectives.
[2] The mean of all 10,000 model iterations.
[3] The individual EVPI (€652) was calculated as the difference between the expected NMB with perfect information and the expected NMB with current information.

The population EVPI was calculated from a healthcare and a societal perspective by multiplying the average individual EVPI values by the number of STHPD patients in the Netherlands who receive the early intervention in the model (n=198,896). The population EVPI values from a healthcare perspective and a societal perspective were plotted against

a range of different WTP thresholds, resulting in a population EVPI curve.

Although the population EVPI provides insight into the NMB gained when having perfect information, it remains unclear which parameters in the model are associated with the greatest uncertainty. If the uncertainty in the current analysis mainly results from the healthcare costs parameters, it might not be worthwhile to further investigate the parameters on treatment effectiveness.

To identify for which parameters future research is worthwhile for both perspectives, we calculated the EVPPI. The EVPPI is calculated as the difference between the expected NMB of a decision made with perfect information on a group of parameters and the expected NMB with current information on that group of parameters. In order to calculate the EVPPI, we performed the model simulations (inner loop) for a fixed randomly drawn value for the parameter(s) of interest given a WTP threshold of €20,000 per QALY. Subsequently, new fixed values of the same parameters were drawn and the simulation was performed again (outer loop). In line with Mohseninejad et al. (6), the number of inner loops was set at 1,000 and the number of outer loops at 100. The simulations were repeated to check for stability of the results. We calculated the EVPPI for the following model parameters or groups of parameters: intervention costs, health-state utilities, utility gain after receiving the early intervention, healthcare costs, the early intervention relative risk that was multiplied with the STHPD to panic disorder transition probability, and the productivity costs (societal perspective only).

Results

Cost-effectiveness

Estimates of the QALYs and costs per treatment alternative are shown in Table 2. Online supplementary file 5.2 shows a scatterplot including the incremental QALYs and costs for the analyses from both perspectives resulting from the 10,000 model iterations. From a healthcare perspective, the ICER of the early intervention versus usual care resulted in €17,144 per QALY gained. The results from societal perspective showed that the intervention was cost-saving, with an ICER of €-16,023 per QALY gained. Figure 1 shows the cost-effectiveness acceptability curves, which shows the cost-effectiveness probability of both treatment options for a range of different WTP thresholds. Given a WTP threshold of €20,000 per QALY, the estimated cost-effectiveness probability for the early intervention was 61% from a healthcare perspective and 93% from a societal perspective.

Table 2: Estimates of discounted costs and QALYs per patient and incremental costs and QALYs

	Mean QALYs (95% CI)	Mean healthcare costs (95% CI)	Mean productivity costs (95% CI)
Additional CBT-based early intervention	3.44 (3.19-3.68)	€8,034 (4,941-11,952)	€50,912 (35,143-70,055)
Usual care	3.28 (3.08-3.47)	€4,934 (2,904-7,481)	€58,004 (42,469-75,931)
Incremental	0.16 (0.02-0.32)	€3,100 (1,002-5,871)	-€7,092 (-18,469-2,997)

Abbreviations: CBT: cognitive behavioral therapy, CI: confidence interval, QALYs: quality adjusted life-years.

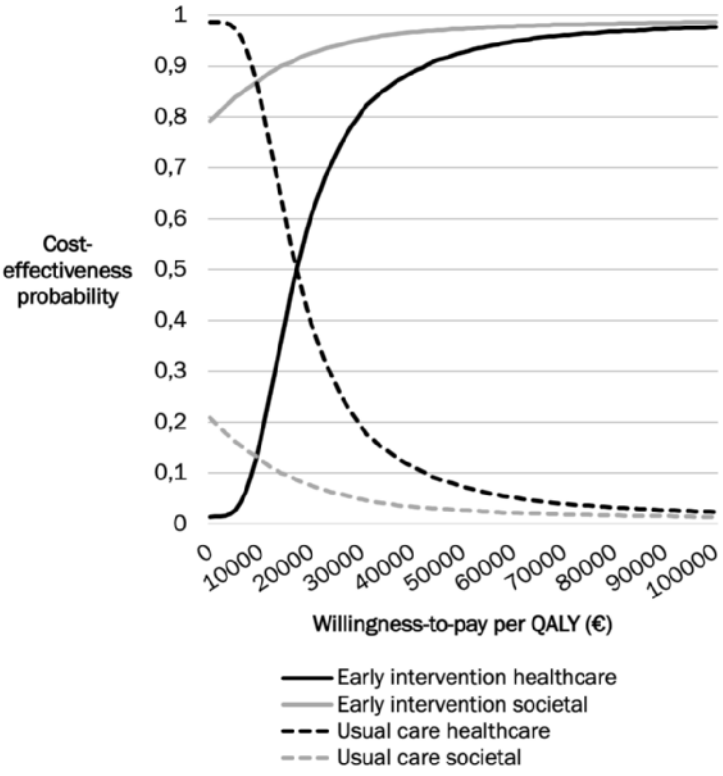

Figure 1: Cost-effectiveness acceptability curve of the additional CBT-based early intervention and usual care

VOI analysis

As an example, Table 1 presents the generated NMBs for both treatment options for six model runs of the CEA from a healthcare perspective. The early intervention had the highest NMB value for the CEAs from both perspectives, and therefore the early intervention was the preferred treatment option. Therefore, no benefits were gained for model runs that identified the early intervention as the treatment option with the highest NMB. The individual EVPI values were €652 from a healthcare perspective and €148 from a societal perspective. Multiplying these values with the target population (n=198,896) resulted in population EVPIs of €129.7 million from a healthcare perspective and €29.5 million from a societal perspective given a WTP threshold of €20,000 per QALY. Reducing all parameter uncertainty was thus valued at a total of €129.7 and €29.5 million, respectively.

Figure 2 presents the estimated population EVPI values from both healthcare and societal perspectives over a range of WTP values. The population EVPI from a healthcare perspective showed a maximum of €141.2 million at a WTP of €18,900 per QALY. At this threshold, decision uncertainty was the highest. The probability that the additional early intervention was cost-effective increased for larger WTP thresholds, and therefore the EVPI decreased. Because the early intervention was expected to be more effective at lower costs from a societal perspective, the cost-effectiveness probability further increased for larger WTP thresholds. As decision certainty increased with WTP, the societal EVPI declined.

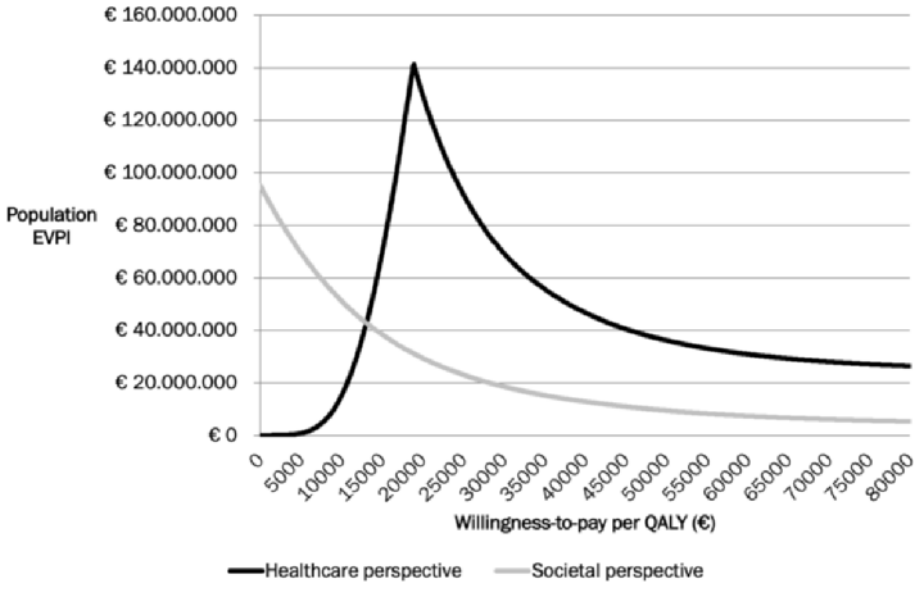

Figure 2: The population Expected Value of Perfect Information (EVPI) for different willingness-to-pay thresholds

The uncertainty of subsets of parameters was valued in the EVPPI given a WTP threshold of €20,000 per QALY (Figure 3). Because the model parameters interact within the model structure and because not all parameters are considered, the EVPPIs do not sum up to the overall EVPIs for each perspective (22, 23). When the CEA is performed from a healthcare perspective, the early intervention utility gain parameter contributed to most of the uncertainty (73% of total EVPI), followed by the intervention cost parameters and the health-state utility parameters (51% and 20% of total EVPI). The population EVPPIs for these groups of parameters equaled €94.9 million, €66.7 million, and €25.8 million, respectively. The EVPPIs for the healthcare cost parameters and the relative risk for the early intervention equaled €21.4 and €15.7 million. When the cost-effectiveness analysis was performed from a societal perspective, the EVPPI of the early intervention relative risk parameter equaled €10.2 million. The EVPPIs for the remaining (groups of) parameters were equal to zero, including the productivity costs, which indicates that there was no expected value of further research into these parameters.

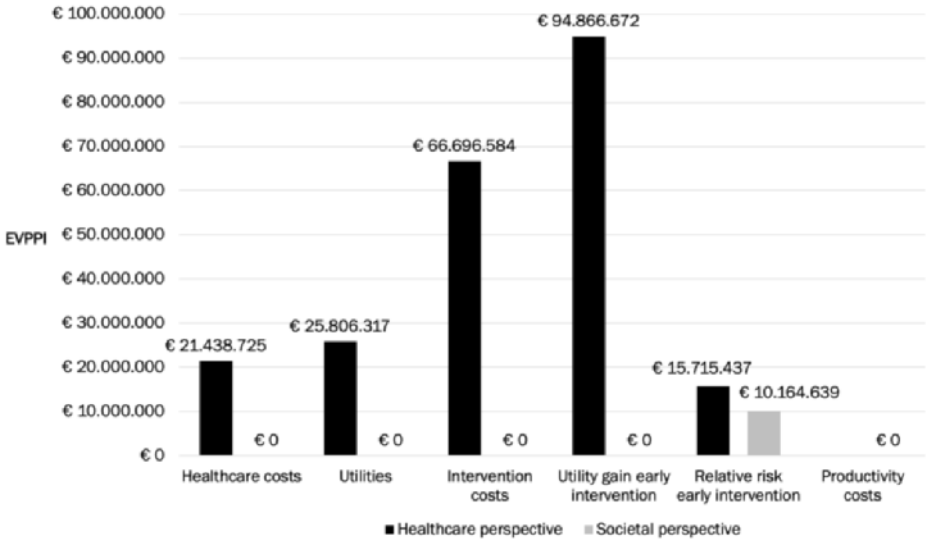

Figure 3: Expected Value of Partial Perfect Information (EVPPI) from both perspectives given a willingness-to-pay threshold of €20,000 per QALY

Discussion

In this study, we aimed to identify research priorities regarding the cost-effectiveness of a CBT-based early intervention for STHPD using VOI analysis and to investigate to what extent priority setting depends on the perspective. The decision uncertainty was relatively high when a healthcare perspective was applied, and eliminating uncertainty was valued at a total of €129.7 million for a WTP of €20,000 per QALY. The decision uncertainty in our model is comparable to other cost-effectiveness analyses on psychological interventions in mental healthcare that applied a healthcare perspective (6, 24). Additional research on the early intervention utility gain in the model was most valuable from a healthcare perspective. However, when a societal perspective was applied, the decision uncertainty was minimal and additional research was expected to have little added value. The EVPI for specific (groups of) parameters (EVPPI) equaled zero from a societal perspective, except for the early intervention relative risk parameters. These results indicate that additional research on the healthcare costs, productivity costs, health-state utilities, early intervention utility gain, and intervention costs considered in the model would not generate value from a societal perspective.

Our results indicate that the cost-effectiveness estimates and the potential value of

additional research substantially differed when we applied a societal perspective instead of a healthcare perspective. From a societal perspective, additional research would generate little additional value whereas further research from a healthcare perspective could be considered worthwhile, especially for the utility gain associated with the early intervention. When healthcare policy makers decide to invest in a CBT-based early intervention for STHPD at a WTP of €20,000 per QALY, the cost-effectiveness probability that the early intervention is cost-effective is only 61%. Because this decision uncertainty is relatively high, reducing decision uncertainty would be beneficial for healthcare policy makers. Investing in additional research on the early intervention utility gain, intervention costs, and health-state utilities in order to reduce uncertainty could be considered. For employers or others investors for whom the societal perspective is relevant, on the other hand, additional research is not likely to be worthwhile as additional information within the probabilistic sensitivity analysis would not generate additional value. It is unlikely that investing in additional research on the parameters included in the VOI will yield extra information regarding the decision from a societal perspective, which emphasizes the importance of identifying the relevant perspective for the CEA.

In a comparable VOI analysis on a minimal intervention for depression (6), however, additional research on the costs outside healthcare generated most value from a societal perspective. Additional research on this model parameter was considered worthwhile. The same WTP threshold of €20,000 per QALY was applied (6). A possible explanation for this difference could be that in our study the intervention was more cost-saving. Consequently, the uncertainty surrounding the non-healthcare costs parameters might have been less influential as even for lower thresholds the early intervention was cost-saving. Another VOI analysis in the field of mental health was applied to an intervention on reducing juvenile delinquency (3). In that study, the healthcare costs and intervention costs were relatively uncertain, which is comparable to our findings from a healthcare perspective. However, comparing results between different CEAs and VOI analyses is difficult because of the different model structures, input parameters, and parameters included in the probabilistic sensitivity analysis and EVPPI.

To our knowledge, our study is the first to apply a VOI analysis to cost-effectiveness research in the field of (subthreshold) panic disorder. A strength of the application of this analysis is that it values the uncertainty surrounding the cost-effectiveness estimate, which provides valuable input for policy decisions regarding investments in future research. There are also some limitations that require discussion. The VOI analysis in this article estimates the value of eliminating the parameter uncertainty of the presented

model, but two other relevant sources of uncertainty may have influenced the results which were not captured by VOI analysis: structural and methodological uncertainty (25, 26).

Structural uncertainty is likely to be present in our model. For example, we did not apply different health-state transition rates for individuals who received any treatment for panic disorder due to a lack of available information (13). Instead, the effectiveness of interventions was reflected in utility gains. It was assumed that patients who received interventions for panic disorder had the same chance of remission as patients who did not receive an intervention (13). Therefore, the effect of the interventions for panic disorder might have been underestimated. We did not calculate the EVPPI for the health state transition parameters since they were fixed. We consider this as a limitation, because in a comparable VOI study the health-state transition rates were the most uncertain (3).

The second source of uncertainty is methodological uncertainty, which relates to the analytical methods used in the model. One aspect related to this uncertainty is the WTP threshold, which requires attention given its importance for our study. We applied a WTP of €20,000 per QALY in our study, which we used for the CEAs and VOI of both health-economic perspectives. However, a WTP of €20,000 is mostly used for a healthcare setting (6, 27). Although the application of different WTP thresholds for CEAs from a healthcare and a societal perspective is uncommon in published CEAs, it has been mentioned that using a different WTP according to perspective might be more appropriate (28, 29). A reason is that from a societal perspective threshold values should reflect the consumption of health from a societal perspective, while from a healthcare perspective WTP thresholds would reflect the marginal value of health provided for by a publicly financed healthcare system, which are not always the same. As it is likely that a societal WTP would be larger than the healthcare WTP and because the addition of productivity costs in a CEA improves cost-effectiveness in most cases we can expect that the cost-effectiveness would always be more favorable from a societal perspective when an intervention is more effective than the comparator. We could therefore expect that the value of additional research as identified by VOI from a societal perspective would decrease as the intervention already has less uncertainty about the most cost-effective option compared to the healthcare perspective.

The effect of the early intervention that was applied in the model was largely based on one trial (n=216) (18). Although our results indicate that from a societal perspective the value of additional research would be minimal compared to the healthcare perspective, it

remains uncertain to what extent the results of this trial can be extrapolated to the general population in the Netherlands. Therefore, additional research investigating the effect of the early intervention is still desirable. VOI is limited to the uncertainty surrounding parameter estimates, but neither the quality nor the interpretation of the parameters is considered. These types of uncertainty are not reflected in the EVP(P)I. Assuming that the choices in our model are a good approximation of reality, additional research is expected to have little additional value from a societal perspective.

In order to incorporate the treatment effect of the early intervention in the transition probabilities, we applied a log-normal distributed relative risk to the STHPD to panic disorder transition. A limitation of our study is that the remaining transition parameters in the model were fixed. However, as the intervention's cost-effectiveness is primarily the result of the intervention's reduction in the STHPD to panic disorder transition, the uncertainty in the other transition rates can be considered of second-order importance.

Although VOI analysis quantifies the value of uncertainty, in general and for specific model parameters, its practical application remains difficult (30). The EVPI is estimated on the assumption that only cost-effectiveness outcomes guide decision making. However, additional decision makers' constraints such as the maximum budget impact and health equity are usually not taken into account (30). For future research and policy decisions on early interventions for panic disorder, it is therefore important that such considerations are identified.

In conclusion, our results showed that research priorities regarding an early intervention for STHPD differed according to the health-economic perspective applied to the CEA. The VOI analysis indicated that additional research to eliminate uncertainty surrounding the cost-effectiveness estimate is worthwhile when the CEA is performed from a healthcare perspective, but less so when a societal perspective was applied. When the probability that an intervention is more effective as well as cost-saving is high, the value of additional research is likely to be minimal. Because performing a VOI analysis is recommended in the new Dutch guidelines for economic evaluations in healthcare (11), a conscious consideration of the health-economic perspective used for CEAs on interventions for panic disorder is therefore important. Our study underlines that the health-economic perspective of CEAs on interventions for panic disorder must be chosen carefully in order to avoid inappropriate choices in research priorities.

Appendices available at www.rhophuis.com

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CHAPTER 7

mHealth coaching on nutrition and lifestyle behaviors for subfertile couples using the Smarter Pregnancy program: a model-based cost-effectiveness analysis

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Abstract

Background. The healthcare costs for reproductive care have increased substantially by the use of technologies such as in vitro fertilization (IVF). The mHealth coaching program Smarter Pregnancy (SP) is an effective intervention to improve fertility-impairing lifestyle behaviors of couples who are undergoing IVF treatment. SP is expected to increase the chance of pregnancy following IVF, which might lower the total IVF costs.

Objective. To evaluate the cost-effectiveness of SP versus usual care in women of subfertile couples starting their first IVF cycle.

Methods. The cost-effectiveness analysis was performed based on information on numbers of participants undergoing IVF treatment at the Erasmus University Medical Center (Rotterdam, the Netherlands) or affiliated clinics. A decision tree model was used to assess the incremental cost-effectiveness ratio (ICER) of ongoing pregnancies and costs of SP versus usual care. A probabilistic sensitivity analysis was performed to consider the uncertainty surrounding the point estimates of the input parameters.

Results. Based on our model that included 793 participants, SP resulted in 86 additional pregnancies and saved €270 thousand compared to usual care after two IVF cycles, with an ICER of -€3,050 (95%CI -3,960 | -540) per additional pregnancy. The largest cost-saving was caused by the IVF healthcare costs avoided. Sensitivity analyses showed that the mHealth program needs to increase the ongoing pregnancy rate with at least 51% after two IVF cycles in order to be cost saving.

Conclusions. SP is an effective and potentially cost-saving mHealth coaching program for women preceding their first IVF treatment. Implementation of this mHealth program in routine preconception care for subfertile couples should be considered given the relatively low costs and promising cost-effectiveness estimates.

Introduction

Since the pioneer work of Edwards and Steptoe, in vitro fertilization (IVF) has become an indelible technology in modern era. Over the years, the success of achieving an ongoing pregnancy after IVF treatment has tremendously increased (1). Still, subfertility remains a worldwide problem affecting approximately 12% of couples of reproductive age (2).
In addition to the medical causes of subfertility, modifiable factors such as poor nutrition and lifestyle impair fertility as well (3). Despite this knowledge, poor lifestyle behaviors are still common in the reproductive population (4). The mHealth coaching program Smarter Pregnancy (SP) was developed to motivate couples to adopt healthy nutrition and lifestyle behaviors preceding IVF treatment. In a randomized controlled trial (RCT), we showed that online coaching of participants on nutrition and lifestyle behaviors resulted in significant improvements of these behaviors (5). Based on previous evidence, it can be expected that such improvements could lead to an increase in ongoing pregnancy rates (6). Since the average healthcare and societal costs of IVF are substantial (7), many IVF costs can be saved when a healthy lifestyle would be adopted. We therefore hypothesize that SP program is cost-effective. We aim to assess the cost-effectiveness of SP compared to usual care in subfertile women preceding their first IVF treatment.

Methods

Study population

The modelled population consists of subferftile women undergoing IVF treatment at the Erasmus University Medical Center (Rotterdam, the Netherlands) and affiliated clinics. Data from the SP RCT were used to model the lifestyle and nutrition behaviors of SP and usual care (5). Participants of SP were coached on five behaviors; vegetables and fruit intake, folic acid supplement use, smoking, and alcohol consumption. The study protocol and primary results of the SP RCT have been published elsewhere (5, 8).

Model

A decision tree model was constructed using Microsoft Excel in order to assess the incremental ongoing pregnancies following the first IVF cycle and the costs of SP versus usual care. Ongoing pregnancy was defined as a vital pregnancy at 12 weeks gestation. Women of subfertile couples who started their first IVF treatment at the Erasmus University Medical Center or affiliated clinics in 2015 entered the model (n=793). A

second IVF cycle was started if the first cycle did not result in an ongoing pregnancy. The pregnancy outcome following the second IVF cycle was the endpoint of the model. This short-term evaluation should therefore be considered a first indication of cost-effectiveness of SP.

Model scenarios

The usual care scenario reflects usual IVF treatment in the Netherlands. We assumed that all women received an elective single embryo transfer (ET). We furthermore assumed that all women in the intervention scenario were invited to use SP (100% coverage). The SP intervention was not offered in usual care scenario (0% coverage). Based on trial data, 70% of the SP participants completed the 24 weeks of coaching (5). Accordingly, the intervention adherence rate in the SP intervention scenario was set at 70%.

Model parameters

Analyses were performed from a healthcare and a societal perspective. The healthcare perspective includes SP intervention costs (9), all costs associated with IVF treatment (e.g. laboratory and hospital costs) and other relevant healthcare costs (e.g. general practitioner visits). The societal perspective includes all healthcare costs plus costs outside the healthcare sector which, in this case, mainly consist of productivity costs (costs due to reduced productivity at work) and out-of-pocket expenditures (e.g. costs for folic acid supplements). The model parameters, including their distributions and sources, are reported in Table 1. Ongoing pregnancy rates after the first and second IVF cycle for the usual care scenario were derived from a previous cost-effectiveness modeling study on IVF strategies (10). The pregnancy rates for women who received SP were based on data from Twigt et al (6). A detailed description of the cost calculations is provided in a previous publication by Fiddelers et al (7). Based on SP trial data (5), we incurred costs for adequate vegetables and fruit intake, folic acid supplement use, smoking, and alcohol consumption (Table 1). All costs were expressed in euros (€) for the reference-year 2016 based on the Dutch price index (11).

Table 1: Model input parameters.

Input parameter	Deterministic value	Probabilistic distribution	Source
Costs IVF (per cycle)			
Hospital costs			
Hormone stimulation – medication	€1,580	Fixed	Fiddelers et al. (7)
Hormone stimulation – hospital care	€331	Fixed	Fiddelers et al. (7)
Ovum pick-up	€596	Fixed	Fiddelers et al. (7)
Lab	€1,339	Fixed	Fiddelers et al. (7)
Embryo transfer (ET)	€316	Fixed	Fiddelers et al. (7)
Other	€295	Gamma	Fiddelers et al. (7)
Other healthcare costs			
General practitioner	€3	Gamma	Fiddelers et al. (7)
Other	€13	Gamma	Fiddelers et al. (7)
Costs outside healthcare [1]			
Sick leave	€569	Gamma	Fiddelers et al. (7)
Leave of absence	€141		Fiddelers et al. (7)
Loss of leisure time	€73	Gamma	Fiddelers et al. (7)
Out of pocket expenditures	€77	Gamma	Fiddelers et al. (7)
Informal care	€32	Gamma	Fiddelers et al. (7)
Other	€22	Gamma	Fiddelers et al. (7)
Intervention costs			
Smarter Pregnancy program costs	€61	Gamma	Luyendijk (9)
Lifestyle costs [1]			
Folic acid supplement use	€64	Fixed	Luyendijk (9)
Healthy nutrition	€113	Fixed	Luyendijk (9)
Smoking	€1,223	Fixed	Based on (17) and (18)
Alcohol consumption	€913	Fixed	Based on (19) and (20)
Pregnancy rates usual care			
First IVF cycle	0.329	Beta	Fiddelers et al. (10)
Second IVF cycle	0.229	Beta	Fiddelers et al. (10)

Pregnancy rate intervention			
First IVF cycle – 65% increase	0.543	Beta	Based on Twigt et al. (6)
Second IVF cycle – 65% increase	0.443	Beta	Based on Twigt et al. (6)

[1] Only included in the analysis from societal perspective.

Cost-effectiveness analysis

The outcome measures were the costs and effectiveness of the two IVF cycles expressed as the number of ongoing pregnancies after two IVF cycles. Incremental cost-effectiveness ratios (ICERs) from healthcare and societal perspective were calculated by dividing the difference in costs between SP scenario and the usual care scenario by the difference in ongoing pregnancies in both scenarios. The ICER represents the estimated costs of one additional ongoing pregnancy.

A probabilistic sensitivity analysis was performed to consider the uncertainty surrounding the point estimates of the model input parameters. Probabilistic distributions were assigned to the parameters (Table 1). Thereafter, 1,000 model iterations were performed by drawing random values from the distributions assigned to the input parameters. The IVF pregnancy rates were assigned a beta distribution and cost parameters were assigned a gamma distribution. We calculated the average costs and ongoing pregnancies by averaging the 1,000 iterations. We performed deterministic sensitivity analyses to investigate the impact of changing several key parameters of the model: the coverage and adherence rate of SP and the chance of an ongoing pregnancy following SP.

Results

Based on our model that included 793 women, the SP scenario resulted in 369 (47%) pregnancies (95%CI 317 | 422) and the usual care scenario resulted in 283 (36%) pregnancies (95%CI 209 | 363) after two IVF cycles (Figure 1). The average healthcare costs for the SP scenario and for usual care were €6,008,460 (95%CI 5,671,030 | 6,505,020) and €6,214,840 (95%CI 5,839,510 | 6,730,290), respectively. The average societal costs for the SP scenario and for usual care were €7,492,380 (95% CI 6,821,300 | 8,369,360) and €7,762,370 (95%CI 7,008,520 | 8,716,840), respectively (Figure 1). The ICERs from healthcare and societal perspective equaled -€2,250 (95%CI -3,030 | -760) and -€3,050 (95%CI -3,960 | -540) per additional ongoing pregnancy. The difference

in average societal costs and healthcare costs is relatively small, indicating that the addition of the non-healthcare costs had no substantial impact on the ICER. Figure 2 shows the cost-effectiveness plane, in which almost all ICERs are located in the south-east quadrant of the plane indicating that SP is cost-saving.

In the deterministic sensitivity analyses (Table 2), SP was cost-saving on average, but the uncertainty surrounding the ICERs increased substantially when the intervention was less effective (i.e. lower increase in ongoing pregnancies). SP should increase the ongoing pregnancy rate with at least 51% in order to be cost-saving (defined as the CI remaining cost-saving) compared to usual care when a 70% SP adherence rate was assumed. Given an increased pregnancy rate of 65%, the adherence to SP should be at least 49% in order to remain cost-saving.

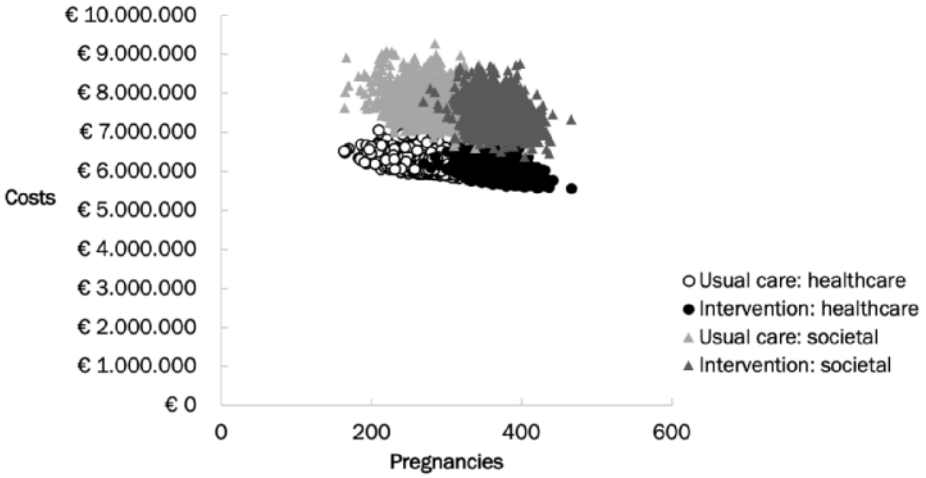

Figure 1: Costs and effects (ongoing pregnancy rate) of the mHealth coaching program Smarter Pregnancy (SP) and usual care, divided in healthcare and societal perspectives.

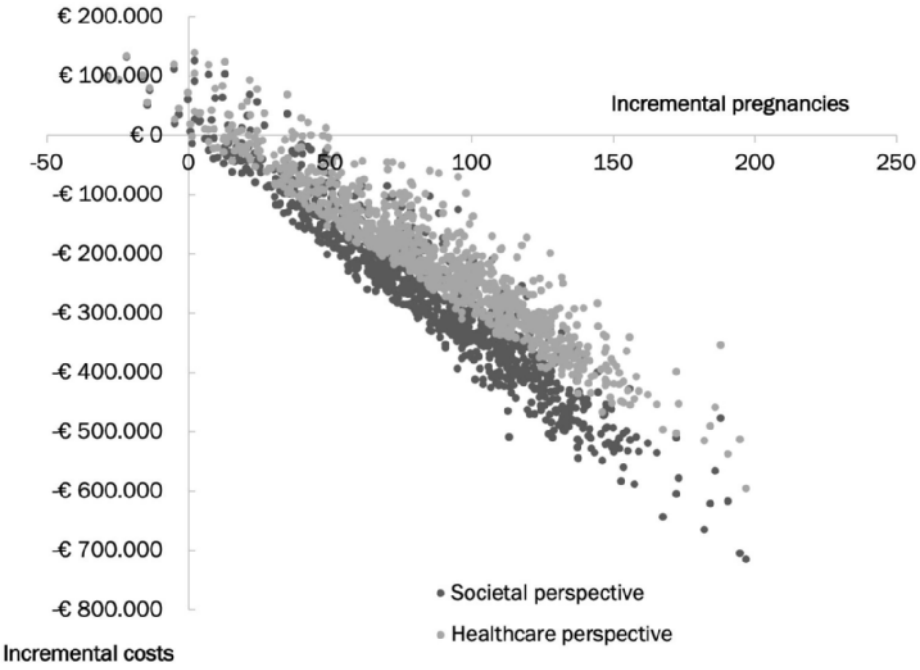

Figure 2: Incremental cost-effectiveness ratios (ICER) generated by 1,000 model simulations, divided in healthcare and societal perspectives.

Table 2: Results of the deterministic sensitivity analyses.

	Mean incremental pregnancies	Mean incremental societal costs	Mean ICER societal perspective (95% CI)
Main analysis [1]	86	-€269,980	-€3,050 (-3,960 | -540)
Sensitivity analyses			
Intervention adherence 85%	105	-€340,230	-€3,210 (-3,960 | -1,630)
Intervention adherence 55%	63	-€192,060	-€2,840 (-3,920 | -120)
Pregnancy rate 45% increase (0.477)	64	-€186,335	-€3,070 (-5,610 | 1,620)
Pregnancy rate 25% increase (0.411)	40	-€98,272	-€2,300 (-9,610 | 9,520)
Intervention	62	-€187,620	-€2,840 (-3,930 | -

coverage 70%			540)
Intervention coverage 85%	74	-€227,420	-€2,850 (-3,900 | -710)
Worst case scenario [2]	21	-€37,310	-€1,270 (-20,870 | 13,240)
Best case scenario [3]	123	-€408,870	-€3,600 (-3,900 | -1,850)

[1] 100% intervention coverage, 70% intervention adherence, 65% increase in pregnancy rate.
[2] 70% intervention coverage, 55% intervention adherence, 25% increase in pregnancy rate.
[3] 100% intervention coverage, 100% intervention adherence, 65% increase in pregnancy rate.

Discussion

Principal findings

This study showed that SP resulted in 86 additional pregnancies and saved €269,980 compared to usual care after two IVF cycles, resulting in an ICER of -€3,050 per additional ongoing pregnancy. SP should increase the ongoing pregnancy rate with at least 51% in order to be cost-saving after two cycles of single ET IVF treatment.

Strengths and limitations

A strength of our model is the combined use of available evidence regarding epidemiology, clinical effectiveness, adherence, and costs in order to support decision making. Ideally, model parameters would be based on meta-analyses or large datasets, but these were unavailable for the current analysis. Since the SP RCT is still ongoing, assumptions had to be made based on a previous periconception cohort study conducted in the Erasmus University Medical Centre, regarding ongoing pregnancy rates, when using this intervention. Our model therefore requires validation when the trial is completed.

In economic evaluations, a time horizon that is long enough to capture all relevant costs and effects is preferred (12). Our study was limited to two IVF cycles, which is relatively short. However, as the aim of our study was to assess the incremental ongoing pregnancies, other costs and effects (i.e. birth complications) were not considered.

Another limitation is that we only assumed single ETs, because in the Netherlands this is the most common strategy for women who start their first IVF treatment. Results of this study only apply to single ETs since costs and ongoing pregnancy rates of other IVF strategies differ (10).

Comparison with literature

Several studies have investigated the effectiveness of nutrition and lifestyle interventions preceding fertility treatment. However, most of these studies focus on specific patient groups, such as obese or anovulatory women (13, 14). In accordance with our findings, the study by Van Oers et al (15) showed that lifestyle intervention (comprising energy-restricted diet, increase in physical activity, and motivational counselling) preceding fertility treatment was cost-effective in terms of achieving an ongoing pregnancy within 24 months. Because nutrition and lifestyle interventions in preconception care have relatively low additional budget impact, we expect that the risk that the SP intervention is not cost-effective would be low (16).

Conclusions

Our results show that SP is potentially cost-saving for subfertile couples preceding their first IVF treatment. Although our results are promising, our model requires validation with the SP RCT data. More research is needed on the pregnancy rates following SP in order to establish the relative cost-effectiveness of the SP with greater certainty. Implementation of the SP program in preconception care should be considered given the relatively low intervention costs and promising cost-effectiveness estimate.

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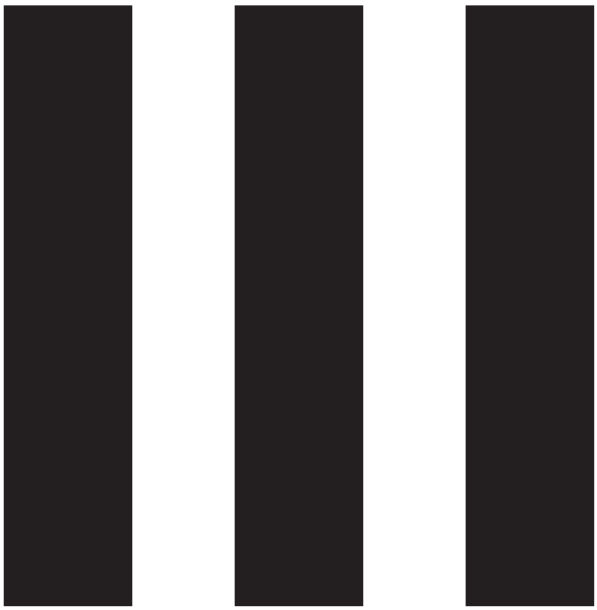

PART III

Health-related quality of life

CHAPTER 8

Health-related quality of life in injury patients: the added value of extending the EQ-5D-3L with a cognitive dimension

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Abstract

Introduction. The EQ-5D is frequently used to understand the development of health-related quality of life (HRQOL) following injury. However, the lack of a cognition dimension is generally felt as disadvantage as many injuries involve cognitive effects. We aimed to assess the added value of a cognitive dimension in a cohort of injury patients.

Methods. We analyzed EQ-5D-3L extended with a cognition (EQ-5D+C) dimension responses of 5,346 adult injury patients. We studied dimension dependency, assessed the additional effect of the cognitive dimension on the EQ-VAS, and, using the EQ-VAS as a dependent variable, determined the impact of EQ-5D and EQ-5D+C attributes in multivariate regression analyses.

Results. Extreme cognitive problems combined with no problems on other dimensions are uncommon, whereas severe problems on other dimensions frequently occur without cognitive problems. The EQ-VAS significantly decreased when cognitive problems emerged. Univariate regression analyses indicated that all EQ-5D+C dimensions were significantly associated with the EQ-VAS. Exploratory analyses showed that using any set of five of the six EQ-5D+C dimensions resulted in almost identical explained variance, and adding the remaining 6th dimension resulted in a similar additional impact.

Conclusions. The addition of the cognition dimension increased the explanatory power of the EQ-5D-3L. Although the increase in explanatory power was relatively small after the cognition dimension was added, the decrease of HRQOL (measured with the EQ-VAS) resulting from cognitive problems was comparable to the decreases resulting from other EQ-5D dimensions.

Introduction

Due to improved survival rates, more individuals experience long term consequences of injury. Assessing variations of health-related quality of life (HRQOL) following injury is valuable to inform patients and to improve quality of care (1). Furthermore, this information provides insight into the patient's perception of recovery and his/her adaptation to the chronic consequences (2, 3).

The EQ-5D is a widely used generic HRQOL instrument which has been validated for both description and valuation of quality of life impact (4, 5). Its concise generic format makes it particularly useful for repeated measurements. However, the question whether dimensions should be added to the EQ-5D from a generic perspective has been debated and researched since its launch in the beginning of the 1990s. These additional dimensions are referred to as bolt-on dimensions (bolt-ons); dimensions that describe additional specific health problems. Krabbe et al. (6) were the first to report that the extension of EQ-5D with a cognitive dimension adds information. Subsequently, several authors suggested valuable bolt-ons, including vision, energy, sleep and skin irritation (7-9). Two recent studies have used systematic approaches to identify possible bolt-ons for the EQ-5D from a range of items, including multiple items related to cognition and memory (10, 11). Both these studies found that cognition is a relevant bolt-on for the EQ-5D, and possibly one of the most important ones (10, 11). However, the relevance of the cognitive bolt-on in injury patients has not been investigated yet, even though cognitive impairments due to traumatic brain injury (TBI) and/or post-traumatic stress symptoms occur relatively frequently in this patient population (12-14).

Our paper addresses the following questions: (a) To what extent are the health impacts on the dimensions related; in particular: does cognition represent a statistically independent dimension?; (b) Do patients with cognitive problems report poorer EQ-VAS scores than patients without cognitive problems?; (c) What is the overall explanatory power of the EQ-5D-3L without and with the additional cognitive dimension using the EQ-VAS score as reference?

Methods

Study population and data collection

We analyzed data of the Dutch Injury Surveillance System (DISS). The DISS gathers data on intentional and unintentional injuries sustained by visitors to the emergency

department (ED) of thirteen hospitals throughout the Netherlands (12-15% coverage) (15). The participating hospitals are a representative sample of hospitals in the Netherlands (16). The ED visits recorded by these hospitals are generally considered to be representative for the total Dutch injury-related ED visits (16). Information that is tracked by the DISS includes the cause, nature and severity of injury, age and sex of the patient and healthcare consumption during hospital admission (e.g. length of stay, admission to the Intensive Care unit). In the DISS hospitals the ED patients are informed about the DISS registry with posters and leaflets that are placed in main patient areas of the ED. The posters and leaflets also explain that participants can withdraw from the DISS registry at any time.

DISS follow up surveys. In 2001-2002 and 2007-2008, follow-up surveys were sent to a stratified sample of ED patients registered in the DISS 2.5 months after their visit to the ED due to an injury. The aim of these follow-up surveys was to collect data on HRQOL, psychological consequences, return to work and healthcare consumption after discharge from the hospital. These data are additional to the data tracked by the DISS. The 2001-2002 follow-up survey was sent to 10,612 patients and the 2007-2008 follow-up to 9,907 patients. Severe and less common injuries were intentionally overrepresented for follow-up. For the follow-up surveys a written informed consent form was sent by mail to the selected sample of ED patients together with the first follow-up questionnaire with the request to read, sign and return the completed questionnaire. The follow-up studies were approved by the Medical Ethics Committee of the Academic Medical Center of Amsterdam. Detailed information about the DISS follow up surveys is presented in the articles by Polinder et al. (15) and Haagsma et al. (17).

Data

EQ-5D outcome data. The EQ-5D is a generic HRQOL instrument (5). The instrument for self-assessment consists of a health classification (the EQ-5D descriptive system), and a subjective health rating (the EQ-VAS) with a score range from 0 (worst imaginable health state) to 100 (best imaginable health state). The EQ-5D descriptive system has five dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression with ordinal response options. The EQ-5D is available in two response versions: the three level version (EQ-5D-3L) and the more recent five level version (EQ-5D-5L). The DISS follow-up surveys used the EQ-5D-3L. The ordinal levels of the EQ-5D-3L version are ‘no problems’, ‘some problems’, and ‘extreme problems/unable to’. With five dimensions and

three levels the system creates 243 potential health profiles. A profile of '11111' represents the best possible health state, whereas the profile '33333' represents the worst possible health state. These health profiles have been valued by representative samples of the general population (18, 19); from their values a value set has been derived allowing the calculation of a utility score for any health profile. We used the value set derived from preferences of the general population of the Netherlands to calculate utility scores (20).

In current DISS follow up surveys, the EQ-5D-3L was extended with a three level cognition dimension covering aspects of memory, understanding, concentration and thinking (6). The text format was similar to that of the other dimensions, applying identical level descriptors. The verbatim presentation of the descriptor for the dimension added to the EQ-5D was as follows "Cognitive functioning, such as remembering, concentrating", with the following levels (1) "I have no impairment of cognitive functioning", (2) "I have some impairment of cognitive functioning", (3) "I have severe impairment of cognitive functioning". The EQ-5D-3L and the additional cognitive dimension (together labeled 'EQ-5D+C') were simultaneously administered. Only respondents with completed EQ-5D+C and EQ-VAS response were selected for analysis.

Supplemental DISS injury data. Apart from EQ-5D outcome data, the DISS follow-up surveys included questions on general socio-demographics, cause and type of the injury according to the EUROCOST type of injury categories, healthcare use, expenditures, return to work (21).

Sociodemographic data. The following socio-demographical data were available: gender, age in years, hospital admission after ED visit, comorbidity, and education level. Comorbidity was present if a patient reported one or more of the following health problems: chronic obstructive pulmonary disease (COPD) or asthma, heart disease including a previous myocardial infarction, previous stroke, diabetes mellitus, hernia, (rheumatoid) arthritis, and cancer. We coded the completion of higher professional education or university education as high education level.

Data-analysis

Dimension dependence. Two related questions are relevant if new dimensions are considered. 1. To what extent are the descriptive scores on the dimensions related (dependent)? (for example: the best level in mobility usually corresponds to best level in

usual activities; or: the level of self-care is never better than the lowest level of any of the other dimensions, a case of dominance; or: no relation beyond chance agreement) 2. Are the contributions of the dimensions to the total utility score related? Note that two dimensions may be strongly related in a descriptive way, while they may still have independent roles in utility terms. Reversely, independent dimensions in a descriptive way, may show strong interaction in utility terms, which may be cancellation or enhancement of the disutility associated with either of them. A new dimension at least should show both additional descriptive power and an independent utility role, preferably also at the non-extreme levels. This paper focuses on descriptive independence, question 1, and tentatively addresses question 2 by analysis of EQ-VAS data (see below). The EQ-VAS was used as a proxy of HRQOL in this analysis.

To check descriptive dependence we created cross tables between pairs of dimensions, specifically checking instances of dominance/subordination of the cognitive dimension. The following procedure was developed. We considered the profiles with level 3 (L3; extreme problems) on one dimension (A) and level 1 (L1; no problems) on another dimension (B). Then we defined 'dominance of dimension A across B' as the presence of *less* combinations of A-L3 & B-L1, than of A-L1 & B-L3, corrected for chance frequency of these combinations. This definition catches 'negative' dominance, defined as the mechanism that dysfunction in dimension A is paralleled by dysfunction in each other dimension, limiting the probability of a high level. In our context 'positive' dominance is of no interest, i.e. a high level of dimension A limits the presence of poor levels elsewhere. The authors formulated hypotheses regarding the dominance of dimensions through discussion. For the cognition dimension, we hypothesized that cognition dominates self-care and usual activities. It was deemed plausible that severe cognitive problems co-occurs with severe problems with self-care and usual activities, but not the other way around. The plausibility of the remaining dimension combinations falls outside the scope of this paper, and are therefore not further discussed. In our data analysis, we first estimated the probability of all possible level 3 and level 1 dimension combinations under independence, based on multiplication of the marginal frequencies of the levels per dimension using the following formula: *Probability (D1_L1| D2_L3) = prevalence (D1_L1) * prevalence (D2_L3),* where D1_L1 is dimension 1 (e.g. mobility) level 1 and D2_L3 is dimension 2 (e.g. self-care) level 3. For instance, if mobility_L3 had a prevalence of 10% and usual activities_L1 had a prevalence of 60%, the estimated expected conditional probability of mobility_L3 and usual activities_L1 is 6%.

Then we listed all prevalent EQ-5D+C profiles of our dataset, and selected among them

the pairs with contrasting results (some pairs qualify for multiple contrasts, e.g. the profile 112313 contains 6 L1-L3 contrasts). We compared the number of L1-L3 vs L1-L3 contrasts for dimension combinations with cognition as one of the two dimensions, and calculated the relative frequency of both contrasts, i.e. the observed frequencies relative to chance frequencies. E.g. cognition level 3 and pain/discomfort level 1 versus pain/discomfort level 3 and cognition level 1). The ratio of the relative frequencies (cognition L1&dimension X L3 as denominator) decides on dominance: if it is 1.0 then dimensions are independent, if it is <1.0 than cognition dominates, if >1.0 then cognition is subordinate. Dimension dependency was additionally investigated by calculating Spearman's rank correlation coefficients between the six EQ-5D+C dimensions.

Effect of cognition level on EQ-VAS. The effect of cognition level on the EQ-VAS was investigated by calculating the average EQ-VAS score for each cognition level irrespective of the corresponding EQ-5D profile. The same step was repeated for EQ-5D profiles with relatively severe and mild problems on the other dimensions, which allowed for direct comparison of the EQ-VAS scores as only the cognition dimension levels differed within the complete EQ-5D+C profiles.

Explanatory power analysis of all dimensions. We then predicted the EQ-VAS score from the EQ-5D dimensions, the cognitive dimension, and the socio-demographic factors. Univariate and multivariate regression analysis was applied. All descriptive EQ-5D+C dimensions were dummy coded (=standard): 'some problems' and 'severe problems' with 'no problems' as reference category. Separate and combined analyses were performed for participants with reported full health (EQ-5D profile of 11111) and without full health because of the combined effect of many respondents reporting to be in full health and the non-linear relations in the upper part of the scale. Only complete responses of the EQ-5D, cognition question, and EQ-VAS were selected for analysis.

Firstly, we performed univariate regression analyses and predicted the EQ-VAS with the EQ-5D and cognition attributes. Subsequently, a multivariate regression analyses model was constructed including the original EQ-5D attributes. In the second step, the cognition attributes were added to the model in order to examine the additive effect. Multivariate regression analysis was also used to assess the explanatory power of any set of combinations of five of the six EQ-5D+C dimensions.

Secondly, the EQ-5D attributes, cognition attributes, and all socio-demographic characteristics were simultaneously offered (forced entry) to a multivariate regression

model explaining the EQ-VAS score. The initial model contained first degree interactions. The backward deletion strategy was employed, starting from a model with 16 variables. We deleted non-significant predictors from the model until only significant predictors remained ($p<0.05$). The regression analyses were repeated for patients with specific injury categories to explore the effect of the cognition dimension among patients with and without traumatic brain injury (clinical known group comparison).
All analyses were conducted using SPSS V.24 (Statistical Package for Social Sciences, Chicago, Illinois, USA).

The following hypotheses were formulated:
1. There are no redundancies and dependency patterns in the dimensions of the EQ-5D-3L, but they may exist when cognition dimension is added.
2. There is no added descriptive value of cognitive information, i.e. the coefficient size of cognitive information (in cross-sectional explanatory analysis) is smaller than that of the least important EQ-5D3L dimension, regardless whether socio-demographics are added.
3. The explanatory power of the EQ-5D+C is higher compared to the EQ-5D in TBI patients due to specific cognitive symptoms after TBI.

Results

Descriptive results

Figure 1 describes the flow chart of the participant selection, follow-up, and response. The combined response rate of the 2001 and 2007 follow-up surveys was 6,194 (37.3%), of which 5,346 (32.2%) had complete responses of the EQ-5D+C and EQ-VAS at 2.5 months follow-up. The characteristics of the respondents are listed in Table 1. Responders were significantly older than non-responders (median age 49.9 versus median age 47.5, $p<0.01$), the proportion females was higher (50.7% versus 43.4%, $p<0.01$) and the proportion of patients admitted to hospital was higher (56.1% versus 46.9%, $p<0.01$).
In total, 150 out of 243 (61.7%) possible EQ-5D profiles were reported. The responses to the dimensions of the EQ-5D+C indicated that the pain/discomfort dimension was most affected at 2.5 months follow-up (62.4% reporting any problems), followed by usual activities (57.6% reporting any problems). The cognitive dimension was the least affected (19.6% reporting any problems). Extreme problems (level 3) were most frequently reported in the usual activities dimension (15.5%), whereas extreme problems were least reported in the mobility and cognition dimensions (both 2.7%). A total of 1419 respondents (26.5%)

reported no problems on any dimension and thus had an EQ-5D profile of 11111. Respondents with a 11111 profile were more likely to be male (61.8% versus 44.8%; p<0.01) and younger (mean age 41.8 years versus 52.9 years; p<0.01), less likely to be admitted to the hospital (30.9% versus 65.2%, p<.01) and had fewer comorbidities (16.8% versus 43.8%, p<0.01).

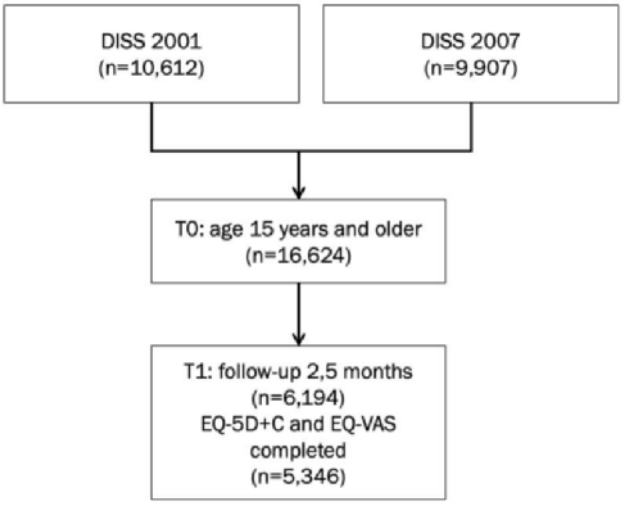

Figure 1: Patient flow chart

Table 1: Characteristics of the respondents aged 15 and older (n=5,246)

Age (mean)	49.9 (SD: 21.5)
Females	50.7%
Hospitalization	56.1%
Length of stay [1] (median, IQR)	4.0 [2.0 – 11.0]
Type of injury	
Skull-brain injury	11.8%
Facial fracture, eye injury	3.9%
Spine, vertebrae	5.0%
Internal organ injury	6.1%
Upper extremity fracture	12.9%
Upper extremity, other	6.4%
Hip fracture	6.8%
Lower extremity fracture	16.1%

Lower extremity, other	9.9%
Superficial injury, open wounds	16.4%
Burns	0.8%
Poisonings	0.8%
Other injury	3.3%

Abbreveations: IQR = Interquartile range, SD: standard deviation.
[1] Median length of stay of patients who were admitted to hospital after their ED visit.

Dimension dependency

Table 2 describes our expectations regarding the likelihood of possible contrasting dimensions. We distinguished likely, unlikely, and very unlikely contrasting dimension levels which were based on agreement between the authors. We defined 'unlikely' as unlikely, but possible in certain cases. Our results showed that all unlikely combinations did occur (0.04-1.31% of all observed combinations). Especially the cognition level 1 and pain/discomfort level 3 was observed relatively frequent (n=132, 2.3% of total observed EQ-5D+C profiles) (Figure 2). We found that level 3 cognition in combination with level 1 combinations on all other dimensions were uncommon (<1%), especially with usual activities. On the contrary, level 1 cognition and level 3 of other dimension combinations occurred more frequent (>1%), especially usual activities level 3 (9.0%). The ratio of the relative frequencies of cognition L3&dimension L1 and cognition L1&dimension L3 was <1.0 for all the dimensions. These findings indicate that cognition is dominant over the other dimensions: extreme cognitive problems and no problems on other dimensions are uncommon, whereas extreme problems on other dimensions frequently occur with no cognitive problems. The Spearman's rank correlation coefficients between the six dimensions ranged from 0.592 (usual activities and pain/other) to 0.223 (mobility and cognition). The Spearman's correlation coefficients between cognition and each of the EQ-5D dimensions was lower than 0.31, except for the dimension anxiety/depression (Spearman's correlation coefficient =0.42). For the other dimensions, only the Spearman's correlation coefficient for mobility and anxiety/depression was lower than 0.31 (Spearman's correlation coefficient =0.30).

Table 2: EQ-5D+C level 1 and 3 combinations, in absolute numbers and expressed as the percentage of total EQ-5D+C profiles (n=5,346)

	M1	SC1	UA1	PD1	AD1	CO1
M3	X	12 (0.22%)	2 (0.04%)	8 (0.15%)	30 (0.56%)	58 (1.08%)
SC3	23 (0.43%)	X	5 (0.09%)	24 (0.45%)	81 (1.52%)	94 (1.76%)
UA3	134 (2.51%)	233 (4.36%)	X	72 (1.35%)	378 (7.07%)	479 (8.96%)
PD3	48 (0.90%)	68 (1.27%)	5 (0.09%)	X	70 (1.31%)	123 (2.30%)
AD3	43 (0.80%)	65 (1.22%)	17 (0.32%)	16 (0.30%)	X	55 (1.03%)
CO3	26 (0.49%)	30 (0.56%)	4 (0.07%)	20 (0.37%)	29 (0.54%)	X

Abbreviations: AD: anxiety/depression, CO: cognition, M: mobility, PD: pain/discomfort, SC: self-care, UA: usual activities.

EQ-VAS by cognition level for various profiles

The average EQ-VAS for each cognition level, combining all profiles given a particular cognition level, is described in Table 3. The EQ-VAS significantly decreased when cognitive problems increased (no problems mean EQ-VAS 74.5 (95% confidence interval (CI) 74.0-75.0); moderate problems EQ-VAS 57.7 (95%CI 56.5-59.0); extreme problems mean EQ-VAS 41.1 (95%CI 37.7-44.4), which showed that cognitive problems are associated with a decrease of the EQ-VAS. The analyses for specific profiles (Table 3) show the same trend, although the decrease of the EQ-VAS was not significant for all profiles, probably due to low sample sizes.

Table 3: EQ-VAS score by cognition level for overall EQ-5D profiles and for exemplary EQ-5D profiles with the most frequently reported level 3 cognition

EQ-5D profile	Cognition level					
	1		2		3	
	n	Mean (95%CI)	n	Mean (95%CI)	n	Mean (95%CI)
All	4298	74.5 (74.0-75.0)	949	57.7 (56.5-59.0)	157	41.1 (37.7-44.4)
11111	1365	85.7 (85.1-85.4)	52	79.9 (76.6-83.2)	2	52.2 (47.6-57.4)
21221	444	70.5 (69.2-71.9)	51	61.6 (57.1-66.0)	2	47.5 (23.0-72.0)
22221	176	63.2 (60.8-65.6)	37	61.2 (56.6-65.8)	2	40.0 (20.4-59.6)
23322	13	46.9 (38.4-55.4)	17	45.7 (39.3-52.2)	15	39.1 (31.4-46.8)
33322	7	40.0 (25.7-54.3)	16	39.2 (33.6-44.8)	9	32.2 (24.5-39.9)
33333	3	18.3 (15.1-21.6)	6	17.5 (1.5-33.5)	10	14.0 (6.3-21.7)

Univariate regression analysis

Univariate regression analyses indicated that all EQ-5D+C dimensions were significantly associated with the EQ-VAS (Table 4). The direction of the relative size of level 2 and level 3 impairments of the same dimension was as expected, with extreme problems on any dimension resulting in greater deficits of the EQ-VAS compared to moderate problems. In univariate analysis, extreme problems with performing usual activities explained most of the variance of the EQ-VAS (17.3%). Moderate and extreme cognitive problems explained respectively 8.7% and 6.2% of the variance of the EQ-VAS. For the non-11111 profiles, moderate and extreme cognitive problems explained both 6.1% of the variance of the EQ-VAS.

For profile 11111 respondents cognition level 2 explained respectively 0.8% of the variance of the EQ-VAS. For cognition level 3 this could not be calculated, since there were only two respondents that reported a 11111 profile and extreme cognitive problems.

Table 4: Association between the EQ-VAS and the EQ-5D and cognition dimensions (univariate analyses)

EQ-5D dimension	R-square	Unstandardized b (95%CI)	p-value
Mobility level 2	0.128	-14.5 (-15.5 to -13.5)	p<0.001
Mobility level 3	0.082	-35.1 (-38.3 to -32.0)	p<0.001
Self-care level 2	0.104	-16.0 (-17.2 to -14.7)	p<0.001
Self-care level 3	0.110	-30.1 (-32.3 to -27.8)	p<0.001
Usual activities level 2	0.035	-7.5 (-8.6 to -6.5)	p<0.001
Usual activities level 3	0.173	-22.9 (-24.2 to -21.5)	p<0.001
Pain/discomfort level 2	0.079	-11.3 (-12.3 to -10.3)	p<0.001
Pain/discomfort level 3	0.104	-30.3 (-32.7 to -27.9)	p<0.001
Anxiety/depression level 2	0.126	-17.1 (-18.3 to -15.8)	p<0.001
Anxiety/depression level 3	0.076	-30.0 (-32.8 to -27.2)	p<0.001
Cognition level 2	0.087	-15.7 (-17.1 to -14.3)	p<0.001
Cognition level 3	0.062	-30.5 (-33.7 to -27.3)	p<0.001

Multivariate regression analysis

The additional cognitive dimension increased the explanatory power of the multivariate model from 45.6% (EQ-5D) to 46.9% (EQ-5D+C). Exploratory analyses showed that using any set of five of the six EQ-5D+C dimensions resulted in almost identical explained variance, and adding the remaining 6th dimension resulted in a similar additional impact (Table 5).

The final model, which explained 48.7% of the variance of the EQ-VAS, included the EQ-5D and cognition attributes and comorbidity. According to the model, having comorbid disease is associated with a significant decrease of the EQ-VAS (Table 6).

Table 5: Explanatory power of multivariate models that included any set of the EQ-5D and cognition dimensions (multivariate analyses)

Selection of EQ-5D+C dimensions	R-square	F-value	p-value
M+SC+UA+PD+AD	0.456	448.1	p<0.01
M+SC+UA+PD+AD+CO	0.469	393.2	p<0.01
M+UA+PD+AD+CO	0.459	453.3	p<0.01
M+SC+PD+AD+CO	0.456	447.3	p<0.01
M+SC+UA+AD+CO	0.448	433.1	p<0.01

M+SC+UA+PD+CO	0.445	427.4	p<0.01
SC+UA+PD+AD+CO	0.454	443.7	p<0.01

Abbreviations: AD: anxiety/depression, CO: cognition, M: mobility, PD: pain/discomfort, SC: self-care, UA: usual activities.

Table 6: Explanatory power of the multivariate model that included the EQ-5D+C dimensions and comorbidity

EQ-5D dimension	Unstandardized b	p-value
Constant	87.4	p<0.01
Comorbidity	-4.0	p<0.01
Mobility level 2	-4.8	p<0.01
Mobility level 3	-16.4	p<0.01
Self-care level 2	-4.2	p<0.01
Self-care level 3	-7.2	p<0.01
Usual activities level 2	-5.6	p<0.01
Usual activities level 3	-10.1	p<0.01
Pain/discomfort level 2	-5.3	p<0.01
Pain/discomfort level 3	-16.1	p<0.01
Anxiety/depression level 2	-7.4	p<0.01
Anxiety/depression level 3	-11.6	p<0.01
Cognition level 2	-6.3	p<0.01
Cognition level 3	-10.9	p<0.01

R-square=0.487, F=192.6

Traumatic brain injury versus other injury

For patients with traumatic brain injury the additional cognition dimension increased the explanatory power of the multivariate model from 55.6% (EQ-5D) to 56.5% (EQ-5D+C). For non-TBI patients this increase was slightly larger, namely from 44.5% (EQ-5D) to 45.8% (EQ-5D+C).

Discussion

Our results showed that extreme cognitive problems and no problems on other dimensions are uncommon, whereas extreme problems on other dimensions frequently occur with no cognitive problems. Moreover, we found that the decrease of HRQOL measured with the

EQ-VAS resulting from cognitive problems was significant. These findings indicate that cognition is dominant over the other dimensions. The additional cognitive dimension increased the explanatory power of the multivariate EQ-5D-3L attributes model from 45.6% (EQ-5D) to 46.9% (EQ-5D+C). This increase is small but similar to adding one of the original EQ-5D dimensions to any set of five EQ-5D+C dimensions.

The performance of the cognition bolt-on has been investigated in previous studies. Krabbe et al. (6) compared valuations (by means of the EQ-VAS) elicited from EQ-5D+C descriptions with parallel EQ-5D descriptions in members of Dutch university staff members. The content validity of the EQ-5D improved by adding cognition. The authors emphasized the importance of considering the inclusion of a cognitive dimension. The employed methods were too crude to quantify the increased explanatory power, however. Wolfs et al. (22) investigated the construct validity and responsiveness of the EQ-5D+C and the EQ-5D in older adults with cognitive impairments using the Mini Mental State Examination (MMSE) as reference. Regarding construct validity, similar correlations between the EQ-5D and the MMSE and between the EQ-5D+C and the MMSE were found, which indicated that there were no differences in construct validity. The EQ-5D and the EQ-5D+C were both responsive to changes in the MMSE, but the EQ-5D performed slightly better. The study of Wolfs et al. (22) is difficult to compare to the results of our study, as the MMSE was used as reference and the increased explanatory power was not investigated.

There does not seem to be consensus as to what increase in R-square is actually meaningful (7). For example, Swinburn et al. (23) reported that the addition of skin-irritation and self-confidence dimensions to the EQ-5D-3L increased the R-square with 22% for psoriasis patients and concluded that the addition of dimensions was much better at predicting outcomes. Whynes (24) reported that the addition of five dimensions increased the explanatory power up to 56%, which was defined a substantial improvement. However, Yang et al. (9) reported that an increase in explanatory power (TTO outcome) of 6% as a result of adding a sleep dimension was not a significant improvement. Compared to these results, an increase in explanatory power of 1.3% is relatively low. However, it is comparable to increase in explanatory power by other EQ-5D dimensions. Moreover, the explanatory power of the multivariate model that included all EQ-5D dimensions was 45.6%. This is in the same order of magnitude as the explanatory power of a multivariate regression model that included the EQ-5D-3L dimensions in community samples (7, 25). This indicates that variation in HRQOL as measured with the EQ-VAS is affected by aspects that are not covered by the current EQ-5D items. This is underlined by

the variation in EQ-VAS scores of respondents with a 11111 profile.

Strengths and limitations

The most important strength of our study is the large number of participants, which allowed for analyses of subgroups, including the additional effect of the cognition bolt-on for specific injury types, without losing statistical power. Furthermore, EQ-5D+C responses were consistent, meaning that extreme problems on any dimension resulted in greater deficits of the EQ-VAS compared to some problems. A limitation of our study is that the follow-up survey was administered 2.5 months post-injury. Many injured patients recover sooner than 2.5 months (15), especially patients with minor injuries such as open wounds, superficial injuries, and contusions. This applies also to mild traumatic brain injury such as concussions in particular, as it is known that cognitive problems are most present within two weeks post-injury (26). Second, a limitation of our study was that the respondents were not a representative sample of the patients who are registered in DISS. Firstly, severe and less common injuries were intentionally overrepresented for follow up. Secondly, young males were less likely to respond to our survey. As a result, the respondents were on average older and the percentage females was higher compared to the patients that were registered in the DISS.

A third limitation of this study is that the EQ-VAS was used as a proxy of HRQOL. A well-known problem of the EQ-VAS is that it is subject end of scale bias; a measurement bias that causes respondents to avoid the extremes of the scale.

In this study we administered the cognitive dimension question immediately after the original EQ-5D and before the EQ-VAS question on the same page. We assumed that participants answered the original EQ-5D questions in the same way regardless of whether the cognition question was included. However, the responses to the original EQ-5D questions may have been influenced by the added cognition questions and the sequence of questions.

Recommendations for future research

For future research, we recommend to investigate the added value of the cognitive bolt-on in a sample of trauma patients shortly after sustaining their injury, e.g. maximally 2 weeks post-injury to ensure that patients are still experiencing symptoms. We also recommend investigating the added value of the cognitive dimension in other patient groups, such as patients suffering from permanent traumatic brain injury, but also in patient groups that have illnesses that are not related to cognitive impairments. We

furthermore recommend to investigate the effects of adding a cognitive dimension to the EQ-5D-5L. The EQ-5D-5L improved the measurement properties and discriminatory power in comparison with the EQ-5D-3L among different patient groups (27). Therefore, it is possible that a cognition bolt-on explains more variance of the EQ-VAS when the EQ-5D-5L is used.

Conclusion

The addition of the cognitive dimension increased the explanatory power of the EQ-5D-3L. Although the increase in explanatory power was relatively small after the cognition dimension was added, the decrease of HRQOL (measured with the EQ-VAS) resulting from cognitive problems was comparable to the decreases resulting from other EQ-5D dimensions.

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CHAPTER 9

General discussion

General discussion

This thesis explores the utilization of HTA in the field of injury, mental healthcare and prevention with the aim of investigating the cost-effectiveness of interventions and improving the methodology of HRQOL measurement in injury patients. This chapter describes the main findings of the research, methodological considerations and implications of this thesis. The chapter ends with recommendations for researchers and healthcare policy.

Main findings

The cost-effectiveness of interventions and methodology of HRQOL measurement in the field of injury, mental healthcare, and prevention were investigated. The thesis consists of three parts with corresponding aims.

Part I: Evidence synthesis

To review the cost-effectiveness of preventive interventions in the field of mental healthcare and injury and to assess the methodological quality of the studies

Two systematic reviews of published economic evaluations were conducted in order to combine health-economic findings regarding falls prevention programs and interventions for anxiety disorders, with the aim to facilitate decision making. *In chapter 2*, we performed a systematic review of economic evaluations of interventions for anxiety disorders. Our review included 42 research articles. The identified interventions for anxiety disorders were divided into pharmacotherapy, psychotherapy, internet-delivered psychotherapy, and combination therapy consisting of both pharmacotherapy and psychotherapy. The economic study designs and outcome measurement were considered appropriate for all studies. The quality scores were variable (38-94%), but good on average (73%). Internet-delivered cognitive behavioral therapy appeared to be cost-effective in comparison with the control conditions. Four out of five studies comparing psychological interventions with pharmacological interventions showed that psychological interventions were more cost-effective than pharmacotherapy. Although the comparability between studies was limited by heterogeneity in terms of interventions, study design, outcome and study quality, the results showed that psychological interventions were more cost-effective than pharmacological interventions.

Another systematic review of economic evaluations was performed for fall preventions programs for older adults (*chapter 3*), including 31 studies. Quality assessment showed that the overall methodological quality was good (84%). Furthermore, there we no significant differences in methodological quality between program types. Our results show that home assessment programs were most cost-effective for community-dwelling older adults. Medication adjustment programs were most cost-effective for older adults living in a residential care facility. The results for mixed populations were more inconsistent. However, exercise, home assessments, and medication adjustment programs were all cost-effective when society is willing to pay more for health gains ($100,000 per QALY). In general, multifactorial programs and other programs were less favorable in terms of cost-effectiveness. Studies that did not report a cost saving or cost-effective program scored a quality of 91% on average, but there was no significant correlation between the quality score and the reported ICERs.

The cost-effectiveness and budget impact of interventions are partly determined by the epidemiology of the specific health problem. It is therefore important to obtain information about prevalence estimates. *Chapter 4* shows an example of estimating the prevalence of acute stress disorder (ASD), post-traumatic stress disorder (PTSD), and depression by means of a systematic review. We specifically investigated the prevalence of these disorders following violence-related injury treated at the emergency department. Fifteen studies reported the prevalence of PTSD following violence related injury, five studies reported the prevalence of ASD, and five studies reported the prevalence of depression. The reported PTSD prevalence estimates differed substantially and ranged between 2% (measured at 6 months post-injury) and 66% (measured at <1 month post-injury). Longitudinal studies on PTSD showed that the prevalence decreased in time, but after 12 months the prevalence increased again. ASD prevalence estimates ranged between 12% and 41% (both measured one week post-injury). The reported depression prevalence ranged between 5% and 41%. Both rates were estimated <1 month post-injury. Heterogeneity resulting from the use of different diagnostic instruments strongly limited the comparability of the reported prevalence. Clear prevalence trajectories could not be identified. The included studies were susceptible to bias due to low response rates and loss to follow-up.

Part II: Cost-effectiveness modeling

To assess the cost-effectiveness of preventive interventions for panic disorder and subfertility and to identify the main drivers of cost-effectiveness using health-economic modeling techniques

The cost-effectiveness of a CBT-based early intervention for patients with subthreshold panic disorder in addition to the usual care for panic disorder was modeled in *chapter 5*. Over a period of five years, usual care resulted in 3.28 QALYs and €59,634 per patient on average, whereas the added CBT-based early intervention resulted in 3.30 QALYs and €59,355 per patient. The ICER equaled €-23,127 per QALY gained, which indicated that the early intervention resulted in more QALYs at lower costs on average in comparison with usual care. Sensitivity analyses showed that the results were robust.

In *chapter 6*, we discussed the role of the health-economic perspective and the expected monetary value of uncertainty of the cost-effectiveness estimates of the CBT-based early intervention for subthreshold panic disorder based on the model presented in *chapter 5*. CEAs and VOI analyses were performed from a healthcare perspective and from a societal perspective. From a healthcare perspective the early intervention was more effective at higher costs compared to usual care resulting in an ICER of €17,144 per QALY, whereas it was cost-saving from a societal perspective. Additional research to eliminate parameter uncertainty was valued at €130 million from a healthcare perspective and €30 million from a societal perspective. Reducing uncertainty in the early intervention utility gain was most valuable from a healthcare perspective (€95 million). From a societal perspective, only the early intervention relative risk parameter generated value (€10 million). Priority setting for future research differed substantially according to the perspective.

In *chapter 7*, we investigated the cost-effectiveness of an online coaching program Smarter Pregnancy (Dutch: Slimmer Zwanger) (SP), a preventive intervention to motivate subfertile women to adopt healthy nutrition and lifestyle behaviors preceding IVF treatment. Based on our model including approximately 800 subfertile women, the SP intervention resulted in 86 additional pregnancies and saved €270 thousand from a societal perspective compared to usual care after two single embryo transfer IVF cycles. The ICER resulted in -€3,050 per additional pregnancy, which indicated that the intervention was cost-saving. The largest cost-savings were caused by the IVF healthcare

costs avoided. Sensitivity analysis showed that the uncertainty surrounding the cost-effectiveness estimate substantially increased when the intervention effectiveness was lower. SP should increase the pregnancy rate with at least 51% in order to remain cost-saving.

We found that preventive interventions in the field of mental healthcare and reproductive care are not only cost-effective, but also potentially cost-saving. As in all modeling studies in this thesis the findings were mainly based on short-term effectiveness data, the long-term cost-effectiveness remains uncertain. We furthermore showed that the perspective of the CEA should be chosen carefully as the results may depend on this choice.

Part III: Health-related quality of life

To investigate the value of alternative approaches for measuring HRQOL in injury patients by means of the EQ-5D-3L

The value of adding a cognitive dimension to the EQ-5D in a cohort of injury patients was investigated in *chapter 8*. Extreme cognitive problems and no problems on other dimensions were uncommon, whereas severe problems on other dimensions frequently occurred without cognitive problems. This finding indicated that cognition is dominant over the other dimensions. The EQ-VAS significantly decreased when cognitive problems were present. Furthermore, univariate regression analyses indicated that all EQ-5D and cognition dimensions were significantly associated with the EQ-VAS. Exploratory analyses showed that using any set of five of the six EQ-5D and cognition dimensions resulted in almost identical explained variance, and adding the remaining sixth dimension resulted in a similar additional impact.

Methodological considerations and implications

Systematic reviews in HTA research

In HTA research, systematic reviews are increasingly used for synthesizing published cost-effectiveness evidence with the aim to inform decision making (1). The number of published economic evaluations of falls prevention (2) and mental healthcare interventions (3, 4) have increased in the past decade. In this thesis, we showed that combining the available evidence provided by individual studies helps identifying which type of interventions for anxiety disorders and falls prevention are the most cost-effective. Furthermore, cost-effectiveness reviews can identify knowledge gaps in terms of health-

economic evidence within these fields. For example, the review of economic evaluations of interventions for anxiety disorders showed that in the majority of the studies a pharmacological intervention was compared to another pharmacological intervention or a psychological intervention was compared to another type of psychological intervention. However, little is known about the cost-effectiveness of pharmacological interventions compared to psychological interventions.

Although systematic reviews can inform decision making in healthcare, it has also been argued that combining health-economic outcomes published in individual studies might be inappropriate because the heterogeneity between studies might hamper interpretation (5). To some extent, the interpretation of systematic reviews of economic evaluations is therefore partially subjective (5). When systematic reviews are used to inform policy, the transferability of health-economic evidence provided by systematic reviews should be verified because the data often originate from different countries and healthcare systems. Applying a transferability check, such as described by Knies et al. (6), would improve the informativity of these reviews for decision making. Investigating the transferability of the studies included in the cost-effectiveness review of this thesis would enhance interpretation of the results as the studies originated from different countries.

In systematic reviews, a critical appraisal of the methodological quality of the included studies provides insight into the potential sources of heterogeneity. We used standardized instruments to assess the methodological quality of the studies included in the reviews (7, 8), but because of the variety of available checklists for assessing health-economic study aspects it remains challenging to properly assess the methodologic quality (8-10). Although we used a consensus-based checklist (CHEC) for assessing the quality of economic evaluations (8), its practical application is limited because it has no standardized scoring instruction. We therefore developed a scoring instruction for the CHEC in order to standardize the quality scoring for the reviews that are included in this thesis. A remaining limitation of the CHEC is that the included items have equal weights in the summary score. Some items (e.g. perspective, time horizon) are expected to have a larger impact on health-economic results than other (e.g. funding statement, discounting). A weighed sum score would enhance the ability to discriminate between high- and low-quality studies (11). Improving the discriminative power of the quality scores is important as high-quality studies tend to report less favorable cost-effectiveness results (12). Therefore, the CHEC could be enhanced when the scoring system would be weighed.

Another pitfall in systematic reviews in HTA is the presence of publication bias. It is known that scientific publications in general are affected by publication bias, which can be

defined as selective publication based on the nature and direction of the results (13). Trials that identify interventions as more effective than the comparator are more likely to be published than trials in which interventions are not effective. In systematic reviews of economic evaluations, the effects of publication bias might even be stronger because cost-effectiveness is introduced as a second factor in addition to effectiveness alone: an effective intervention is not necessarily cost-effective. Indeed, the majority of published cost-effectiveness analyses report favorable incremental cost-effectiveness ratios (12).
Although we identified the most cost-effective interventions for anxiety disorders and falls prevention, the results of the reviews should be interpreted with caution considering the methodological challenges discussed. Despite the drawbacks of using systematic reviews in HTA, these reviews do allow for a more objective appraisal of the published evidence. If they are well conducted, they may resolve uncertainty and inform healthcare policy. Guidelines on how to perform systematic reviews of economic evaluations have been published recently (1, 14, 15), which can contribute to quality improvement and enhancement of the usability of the joint results of economic evaluations.

Uncertainty in health-economic modeling

An important challenge in health-economic modeling relates to the use of trial data as model input. All relevant costs and effects cannot be observed directly in trials, especially in the field of prevention. Trials often have a relatively short time horizon and they are often performed from a healthcare perspective. It is therefore likely that important costs and other relevant effects of preventive interventions remain undetected due to short time horizon or because these costs fall outside the aim of the study. The trial that was used to estimate the effectiveness of the early intervention for subthreshold panic disorder (*chapter 5*) had a relatively short follow-up of 6 months. It therefore remains uncertain to what extent the effect of the intervention (i.e. lowering the transition from subthreshold to full-blown panic disorder) lasts. When the effects are persisting over time, the cost-effectiveness could be more favorable. When the intervention effect is waning over time, the cost-effectiveness could be less favorable as the majority of the patients eventually will develop a full-blown panic disorder regardless whether they received the early intervention. Because trial data often serves as input for modeling, which is generally used to assess long-term cost-effectiveness, there will be an inevitable discrepancy between available data on costs and effects and the most appropriate time horizon for model-based CEAs. In the cost-effectiveness models in this thesis, we applied short-term effects over a longer period than they were measured, which is a limitation of these models. Long-

term data are needed to validate the results generated by the models, especially for preventive interventions.

Because the budgets for research are scarce they are mostly spent on short-term studies rather than long-term studies. A solution is extrapolating short-term outcomes by means of mathematical modeling. Because such an approach takes a lot of effort as this requires sufficient high-quality data, we recommend that researchers should invest more in joint modeling projects in which basic models are developed. Such models allow for expansions and adjustments that can help answering specific research questions. The Chronic Disease Model developed by the Dutch National Institute for Public Health and Environment (16) and the Practical Application to Include Disease Costs (PAID) model by Van Baal et al. (17) are good examples of such models.

Health-economic modeling techniques represent a widely used analytic framework to generate cost-effectiveness estimates based on available data in which the uncertainty surrounding the modelled data is incorporated (18). From a policy perspective, health-economic models are not only used to calculate cost-effectiveness, but also to systematically examine and value the uncertainty surrounding the cost-effectiveness estimates and to identify the sources of uncertainty (19). Uncertainty surrounding the individual model parameters should be incorporated in the models (a probabilistic sensitivity analysis). Furthermore, the impact of changing the value of a single model parameter on the results should be examined (a deterministic sensitivity analysis). The systematic reviews of economic evaluations of falls prevention programs and interventions for anxiety disorders in this thesis show that these types of sensitivity analyses are not always performed in published economic evaluations. In future health-economic models, these types of sensitivity analyses should be performed to increase the quality of the health-economic evidence.

Next to assessing the cost-effectiveness probability by means of sensitivity analyses, another type of uncertainty analysis serves an important purpose which is increasingly recognized: the financial risk of choosing or reimbursing interventions given the current decision uncertainty (18). In case an intervention in reimbursed given a relatively low cost-effectiveness probability (e.g. 60%) based on current evidence, there is a reasonable chance (40%) that a 'wrong' choice is made (i.e. the intervention is actually not cost-effective). Value of information (VOI) can estimate the financial risk of this decision. VOI analyses have mainly been applied to drugs rather than preventive interventions and mental health interventions. For drugs, analyses from a payer's or healthcare perspective are often relevant, whereas the societal perspective is particularly relevant for prevention

and mental healthcare (20) because the majority of the relevant costs often fall outside healthcare (21).

In this thesis, we showed that it is also feasible and relevant to perform VOI analyses for preventive interventions. Because the financial risk of reimbursing the early intervention for panic disorder given the current decision uncertainty for both perspectives differed substantially, we showed the importance of identifying the relevant perspective for CEAs.

Policy makers agree on the advantages and importance of VOI (22), but VOI alone is not sufficient to decide to perform additional research or to reimburse an intervention given the current decision uncertainty. Because the VOI framework is rather complex, practical guidance is needed to use VOI in decision making. Although examples of facilitating the use of VOI have been published, such as applying decision makers' constraints on the outcome of VOI (e.g. a maximum acceptable budget impact of an intervention) (23), the usability of the results needs to be further developed. A comprehensive manual including examples and guidelines for the practical execution and application of VOI would facilitate the use of VOI in decision making. Because VOI analyses are recommended in the recently updated Dutch health-economic guidelines developed by the National Health Care Institute, a VOI manual could be added to the health-economic guidelines.

In *chapter 6*, the utility gain resulting from early intervention resulted in the highest EVPPI. Policy makers could decide to perform affitional research with the aim to reduce uncertainty related to the utiligy gain. In order to know whether it is worthwhile to perform this research, for example by means of an RCT, an estimate of the costs of this RCT is needed. Performing an RCT has no added value when the costs of this RCT exceed the utility gain EVPPI value, but it potentially does when these costs are lower than the EVPPI. Currently there are no standardized estimates of such research costs available for the Dutch healthcare setting, however. Recently, a first attempt to develop a tool for estimating research costs in order to inform VOI analysis has been made (24), but this work should be further developed for general use.

The role of HTA in decision making

HTA research helps policy makers to choose which interventions yield the most health gains at acceptable costs. The practical application of HTA research in healthcare policy is increasing (25), but the development and implementation of decision tools could still be improved (26). To strengthen the value of HTA research, the outcomes must be in line with the information that policymakers need in order to make informed choices for reimbursement and implementation of interventions.

As a result of the increasing healthcare expenditures, not only national decision makers or reimbursement agencies are faced with budget constraints, but also clinicians and other healthcare providers (27). Involving clinicians in deciding on the optimal use of limited resources in an attempt to increase efficiency is therefore crucial. Health-economic evidence is increasingly incorporated in clinical guidelines (27), which are often developed by clinician representatives. As these guidelines are developed to identify the most effective treatment pathways, they are very suitable for promoting cost-effective clinical practice. In the new Dutch treatment standards for mental healthcare (Zorgstandaarden GGZ) (28), health-economic evidence is incorporated in all recommendations. *Chapter 2* and *3* in this thesis are incorporated in the Dutch treatment standard for anxiety disorders (Zorgstandaard Angstklachten en Angststoornissen) (29), which shows that is feasible to include such evidence in clinical guidelines. Including health-economic evidence in guidelines not only ensures awareness of cost-effectiveness among policy makers, but also among clinicians.

Although HTA is increasingly used for decision making in healthcare, policy makers and HTA researchers currently experience different barriers and facilitators regarding the practical application of HTA (30). Policy makers identified a negative or unsupportive attitude of stakeholders (such as healthcare providers or medical professional associations) towards HTA as the most important barrier of using HTA, whereas HTA researchers considered the absence of a framework for decision making as the most important barrier (30). A framework for decision making could be a model with a user-friendly interface that can be used by policy makers to inform decision making. An example of such a framework is the European study on the Quantifying Utility of Investment in Protection from Tobacco (EQUIPT) model (26), in which the cost-effectiveness of different smoking cessation strategies can be investigated for different European countries. This discrepancy between the views of HTA researchers and policy makers draws attention to the need of an explicit framework for decision making that is supported by policy makers, HTA researchers and other relevant stakeholders.

The model-based CEAs in this thesis are focused on interventions that are currently not (systematically) provided (early intervention for panic disorder and online coaching program for subfertile women). However, it would also be beneficial to assess and identify the benefits of investing in cost-effective interventions that are not provided sufficiently within the current healthcare setting or disinvesting in ineffective or inappropriate interventions that are currently provided in the field of prevention, injury and mental health. For example, our systematic review of falls prevention programs showed that

multifactorial falls prevention programs have more unfavorable ICERs compared to the other programs. In order to improve cost-effectiveness, policy makers could consider to disinvest in the implementation of multifactorial programs and to invest in more cost-effective programs such as exercise or medication adjustment programs. As financial resources in healthcare are always limited, investments in the implementation of new interventions are often accompanied by budget cuts for other interventions. To date, little research on disinvesting has been performed (5). In order to improve the efficiency of healthcare systems, it is important that both new investments and disinvestments are considered.

A large part of the current healthcare expenditures increases can be attributed to curative care, in particular new drugs (31). Recently, negative recommendations for the reimbursement of certain drugs such as fampridine and nusinersen (32, 33) have become more common because the ICERs are expected to be unacceptably high. In this thesis, we showed that it is important that policy makers should also focus on reimbursement of non-curative care because preventive interventions have the potential to yield health benefits while costs can be saved. Since 2019, lifestyle interventions for obesity are reimbursed in the Netherlands (34), which shows that the need and importance for preventive and lifestyle interventions are increasingly recognized. The research presented in this thesis justifies the increased attention for reimbursement and implementation of preventive interventions such as Smarter Pregnancy and early interventions for anxiety disorders.

Cost-effectiveness and HTA are not a golden standard, but should merely be seen as a starting tool for guidance. It is important that other aspects such as equity and ethics are also considered in decision making. This requires active involvement of relevant stakeholders in reimbursement decisions, such as HTA experts, medical professional organizations, ethicists, patient representatives and care providers.

Health-related quality of life

The effects of healthcare interventions can be expressed in clinical outcomes, but also in generic outcomes reflecting HRQOL. Clinical outcomes are relevant for specific diseases, but they do not allow for comparison between other health conditions. In theory, the advantage of generic outcome measures such as the EQ-5D is the ability to measure HRQOL across all diseases and interventions. The validity, responsiveness and psychometric performance of the EQ-5D are good for various diseases and conditions (35-38). However, for conditions such as mental disorder and populations such as older adults, which are part of this thesis (39, 40), concerns about the appropriateness of these

measures remain because the convergent validity was generally poor and/or inconsistent. Convergent validity refers to the strength of association between the EQ-5D and other measures (disease specific, symptom or functional measures). Furthermore, a limited number of health-related problems identified by people with mental health problems are currently captured in the EQ-5D, such as fatigue, attention deficit, or social withdrawal (40, 41).

Recently performed principal-component and factor analyses aimed to identify relevant aspects of HRQOL support the finding that the EQ-5D might not cover all relevant of HRQOL (35). Psychological symptoms, physical functioning and pain are covered by the current EQ-5D, but other relevant dimensions consisting of satisfaction, cognition, relationships, hearing, vision, energy and sleep were not. It is therefore relevant that the addition of such dimensions to the current EQ-5D are investigated in future research, also for different populations and patient groups. One approach to improve HRQOL measurement is to expand the widely used EQ-5D questionnaire with additional dimensions (bolt-ons) (42) as we demonstrated in this thesis.

Additionally, concerns have been raised about the appropriateness of using the EQ-5D for older adults because aspects such as independence and social participation are not included in the EQ-5D (39). These aspects are especially important for older adults with fall-related injuries. However, one could argue that aspect like independence and social participation are not part of HRQOL, but quality of life in general. Before considering such dimensions in research, for example as EQ-5D bolt-ons, consensus on the definition and limits of the HRQOL concept is required.

The addition of EQ-5D bolt-ons may ensure that the benefits of healthcare interventions are adequately reflected in QALY estimates for economic evaluations not only in injury but in all conditions. Therefore, the performance of different bolt-ons should be examined extensively in different patient populations before it will be used in practice. For example, our research in this thesis showed that cognition explained little additional variance of the EQ-VAS in injury patients. However, it remains uncertain how much of the variance needs to be explained in order to be meaningful as a bolt-on. Before using EQ-5D bolt-ons, researchers should therefore reach consensus about the meaningful difference in explained variance.

The practical application in HTA research remains challenging because new value sets or tariffs have to be developed in order to deduct utilities from EQ-5D summary scores. It is therefore important that only meaningful bolt-ons are considered for specific patient populations. Currently, tariffs are only available for the current EQ-5D. For every bolt-on

that is introduced, a new tariff has to be developed in order to deduct utilities. Because the development of such tariffs is time consuming and costly, specific bolt-ons (e.g. cognition, sleep) that improve HRQOL measurements the most among different patient groups should be identified first.

When EQ-5D and specific bolt-on tariffs are available, researchers should consider including a bolt-on for deriving utilities in CEAs when it is expected that the EQ-5D does not capture all relevant HRQOL aspects for a specific condition. In order to check whether a bolt-on is relevant, both the EQ-5D+bolt-on and disease-specific HRQOL instruments can be included in CEAs. When the HRQOL results of the EQ-5D (without bolt-on) strongly deviates from the disease-specific HRQOL, the bolt-on could be considered when deriving utilities.

Adding dimensions to the EQ-5D is one way to improve HRQOL measurement, but one could also use other generic HRQOL instruments such as the widely used SF-36 or HUI (43, 44). Because health-economic guidelines in the Netherlands but also in the United Kingdom recommend to use EQ-5D derived QALYs as outcome, problems might arise when using different HRQOL instruments. Using generic HRQOL instruments other than the EQ-5D will decrease comparability of CEAs as it is not in line with current health-economic guidelines. In case the EQ-5D is expected to be inappropriate for a particular condition, mapping SF-36 scores to an EQ-5D index by means of a mathematical model could be a solution (45). However, such approaches should be avoided as much as possible because it might introduce bias in terms of indirectness. It is clear that the EQ-5D and other generic HRQOL instruments have their limitations and that solely depending on current existing measures may not be the right way to evaluate healthcare interventions in the field of injury, but also in general. More research on HRQOL measurement is needed as responsiveness issues may directly impact cost-effectiveness estimates and reimbursement decisions.

Dissemination and societal impact

Performing scientific research is only the first step in achieving a cost-effective and efficient healthcare system. Sharing the findings of this thesis with fellow researchers and clinicians is an important step to stimulate dissemination. Various studies in this thesis have been presented at national and international conferences, such as the Society for Medical Decision Making, the Lowlands Health Economics Study Group, and the national falls symposium (Valsymposium). The next step is to reach out to stakeholders in order to disseminate the findings of scientific research.

The consideration of health-economic evidence in clinical guidelines is an example of involving relevant stakeholders. *Chapter 2* and *3* of this thesis are incorporated in the Dutch treatment standard for anxiety disorders (Zorgstandaard Angstklachten en Angststoornissen) (29), which raises awareness of cost-effectiveness among clinicians. Because health-economics is becoming increasingly important in decision-making, such considerations are necessary.

Recommendations

Recommendations for researchers

- Design, conduct, and report cost-effectiveness studies in conformity with the current health-economic guidelines in order to increase the quality of the health-economic evidence and the comparability between studies
- Perform economic evaluations alongside effectiveness trials within (preventive) healthcare
- Include productivity costs and costs outside the healthcare in cost-effectiveness analyses of interventions in mental healthcare, injury and prevention
- Report negative results of economic evaluations of interventions in order to reduce publication bias
- When decision uncertainty is present, performing a Value Of Information (VOI) analysis might help to identify the financial risk of reimbursing an intervention given the current decision uncertainty and to identify potential research priorities
- Develop guidelines for using VOI and how to communicate the results to policy makers
- Develop user friendly decision tools to facilitate the translation of health-economic evidence into policy advice. Examples are models in which policy makers can compare different policy scenarios.
- Investigate the long-term costs and effects of interventions, for example by joint modeling projects
- Further investigate the additional value of adding bolt-on dimensions to the EQ-5D questionnaire in order to capture relevant aspects of health-related quality of life, especially for older adults

Recommendations for healthcare policy

- Actively involve researchers in establishing preconditions of policy advice
- Consider VOI analysis to determine whether reimbursement of an intervention is acceptable given the current decision uncertainty or determine whether further research is necessary
- Consider investing in the implementation of cognitive behavioral therapy based early interventions for subthreshold panic disorder
- Consider investing in falls prevention programs for older adults
- Take the societal perspective into account when making policy decisions regarding preventive interventions

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SUMMARY

Introduction

In the Netherlands, the healthcare expenditures have increased rapidly over the last decades. The care for mental disorders and hospital care account for most of the healthcare expenditures. The resources in healthcare are limited, and therefore it is necessary that policy makers reimburse interventions that maximize health gain at acceptable costs. Health technology assessment (HTA) is a research field that is concerned with informing policy makers about prioritization and reimbursement of interventions in healthcare. HTA research can clarify how the effectiveness and costs of (new) interventions relate to the effectiveness and costs of other interventions.

This thesis explores the utilization of HTA in the field of injury, mental healthcare and prevention with the aim of investigating the cost-effectiveness of interventions and improving the methodology of health-related quality of life (HRQOL) measurement in these fields.

We focused on three important topics in HTA research. In part I, we focused on the systematic collection and quality appraisal of cost-effectiveness evidence of interventions. In part II, we combined available evidence on epidemiology, costs, HRQOL, and effectiveness of preventive interventions in order to model the cost-effectiveness and to identify the main drivers of cost-effectiveness and uncertainty. Part III covers methodological aspects of HRQOL measurement by means of the EQ-5D-3L in injury patients. The aims of thesis were addressed in separate parts:

1. To review the cost-effectiveness of preventive interventions in the field of mental healthcare and injury and to assess the methodological quality of the studies **(Part I: Evidence synthesis)**
2. To assess the cost-effectiveness of preventive interventions for panic disorder and subfertility and to identify the main drivers of cost-effectiveness and uncertainty using health-economic modeling techniques **(Part II: Cost-effectiveness modeling)**
3. To investigate the value of alternative approaches for measuring HRQOL in injury patients by means of the EQ-5D-3L **(Part III: Health-related quality of life)**

Part I: Evidence synthesis

This thesis contains two systematic reviews of economic evaluations of interventions in healthcare, and one systematic review on the prevalence of mental disorders following

violence-related injury. In *chapter 2* we performed a systematic review of economic evaluations of interventions for anxiety disorders. We identified 42 relevant studies. The interventions were categorized into pharmacotherapy, psychotherapy, internet-delivered psychotherapy, and combination therapy consisting of both pharmacotherapy and psychotherapy. Internet-delivered cognitive behavioral therapy was cost-effective in comparison with the control conditions. Although the comparability between studies was limited by heterogeneity in terms of interventions, study design, outcome and study quality, the results showed that psychological interventions were more cost-effective than pharmacological interventions. The economic study design and outcome measurement of all included studies were considered appropriate, but the methodological quality of the individual studies was variable.

In *chapter 3* we systematically reviewed the literature on economic evaluations of falls prevention programs for older adults. Thirty-one studies were included. We applied a societal willingness-to-pay threshold of $50,000 per quality-adjusted life year (QALY), which means that it was assumed that society is willing to pay $50,000 for an additional life year in full health. For community-dwelling older adults home assessment programs were most cost-effective. Medication adjustment programs were most cost-effective for older adults living in a residential care facility. The results for mixed populations were inconsistent, however. When the societal willingness-to-pay increased ($100,000 per QALY), falls prevention programs consisting of exercise, home assessments, and medication adjustment programs were all cost-effective. Multifactorial programs and other programs were less favorable in terms of cost-effectiveness. The overall study quality was good (84%), and there was no significant correlation between the quality score and the reported incremental cost-effectiveness ratios (ICERs).

In *chapter 4* we aimed to provide an overview of the published literature reporting the prevalence estimates and trajectories of post-traumatic stress disorder (PTSD), acute stress disorder (ASD), and depression following violence related injury treated at the emergency department, and to assess the quality of the studies included. We performed a systematic review, which identified sixteen relevant studies. Fifteen studies reported the prevalence of PTSD following violence related injury, five studies reported the prevalence of ASD, and five studies reported the prevalence of depression. The reported PTSD prevalence estimates differed substantially and ranged between 2% (6 months post-injury) and 66% (<1 month post-injury). Longitudinal studies on PTSD showed that the

prevalence decreased in time, but after 12 months the prevalence increased again. ASD prevalence estimates ranged between 12% and 41% (both measured one week post-injury). The reported depression prevalence ranged between 5% and 41%. Both rates were estimated <1 month post-injury. Clear prevalence trajectories could not be identified. Heterogeneity resulting from the use of different diagnostic instruments strongly limited the comparability of the reported prevalence estimates, and the included studies were susceptible to bias due to low response rates and loss to follow-up.

Part II: Cost-effectiveness modeling

Chapter 5 describes a cost-effectiveness model of a cognitive behavioral therapy based early intervention for subthreshold panic disorder. The model was designed to assess the cost-effectiveness of adding the early intervention to the usual care for panic disorder in the Netherlands. Adding the early intervention to the usual care for panic disorder resulted in 3.30 QALYs and €59,355 per patient on average after five years. Usual care alone resulted in 3.28 QALYs and €59,634 per patient. The ICER from a societal perspective equaled €-23,127 per QALY gained. The sensitivity analyses showed that the results were robust. In *chapter 6* we aimed to identify research priorities regarding the cost-effectiveness of the early intervention using value of information (VOI) analysis. In addition, we investigated to what extent priority setting depended on the perspective. The early intervention was cost-saving from a societal perspective, but it was not from a healthcare perspective. From a healthcare perspective, the ICER resulted in approximately €17,000 per QALY. Additional research to eliminate parameter uncertainty was valued at €130 million from a healthcare perspective and €30 million from a societal perspective for the whole population. Priority setting for future research differed substantially according to the perspective.

Another cost-effectives model was developed for assessing the cost-effectiveness of an online coaching program Smarter Pregnancy (SP), a preventive intervention to motivate subfertile women to adopt healthy nutrition and lifestyle behaviors preceding in-vitro fertilization (IVF) treatment in the Erasmus University Medical Center (*chapter 7*). The analysis was performed from a societal perspective, and the number of pregnancies and the societal costs were used as model outcome. Among the study population of approximately 800 subfertile women, SP resulted in 86 additional pregnancies and saved €270 thousand from a societal perspective compared to usual care after two single

embryo transfer IVF cycles. The ICER equaled -€3,050 per additional pregnancy, which indicated that the intervention was cost-saving. The largest cost-savings were caused by the IVF healthcare costs avoided. The sensitivity analysis showed that the uncertainty surrounding the cost-effectiveness estimate substantially increased when the intervention effectiveness was lower.

Part III: Health-related quality of life

The value of adding a cognitive dimension to the EQ-5D-3L questionnaire for measuring health-related quality of life (HRQOL) was investigated in a cohort of injury patients (chapter 8). We found that extreme cognitive problems and no problems on other dimensions were uncommon, whereas severe problems on other dimensions frequently occurred without cognitive problems. The EQ-VAS significantly decreased when cognitive problems emerged. Furthermore, univariate regression analyses indicated that all EQ-5D and cognition dimensions were significantly associated with the EQ-VAS. Exploratory analyses showed that using any set of five of the six EQ-5D and cognition dimensions resulted in almost identical explained variance, and adding the remaining sixth dimension resulted in a similar additional impact.

Discussion

The aim of this thesis was to explore the utilization of HTA in the field of injury, mental healthcare and prevention with the aim of investigating the cost-effectiveness of interventions and improving the methodology of HRQOL measurement in these fields.
We showed that combining the available health-economic evidence provided by individual studies helps identifying which type of interventions for anxiety disorders and falls prevention are the most cost-effective. Considerable methodological variation existed between the published economic evaluations within these fields, which hampered comparison of the results. We therefore showed the importance of designing, conducting, and reporting cost-effectiveness studies in conformity with the current health-economic guidelines in order to increase the quality of the health-economic evidence and the comparability between studies.

In this thesis, we used health-economic modeling techniques to calculate the cost-effectiveness of interventions and to examine and value the uncertainty surrounding the

cost-effectiveness estimates. The financial risk of choosing an intervention given the current decision uncertainty was quantified using VOI. These values strongly depended on the perspective of the CEA. Our research underlines that the health-economic perspective that is applied in economic evaluations (e.g. healthcare perspective and the societal perspective) should be chosen carefully, as the cost-effectiveness can be more favorable when the costs outside the healthcare sector are considered. This is particularly true for preventive interventions. However, it is challenging to model all relevant data because they are often not available, especially long-term data. Therefore, we recommend that joint modeling projects should be a research priority. Easily accessible basic models containing high quality and long-term data should be developed, because such models allow for expansions and adjustments that can help answering specific research questions.

The addition of EQ-5D bolt-ons may ensure that the benefits of healthcare interventions are adequately reflected in QALY estimates for economic evaluations. We showed that the addition of the cognition dimension increased the explanatory power of the EQ-5D-3L among injury patients. However, more research on cognition and other bolt-ons is needed to justify the addition of a cognitive dimension when measuring HRQOL with the EQ-5D-3L among these patients. The EQ-5D has its limitations and solely depending on existing measures may not be the right way to evaluate healthcare interventions in the field of injury, but also in general. More research on HRQOL measurement is needed because responsiveness issues may directly impact cost-effectiveness estimates and reimbursement decisions.

SAMENVATTING

Introductie

In Nederland zijn de uitgaven voor de gezondheidszorg in de afgelopen decennia snel gestegen. De zorg rondom psychische stoornissen en ziekenhuiszorg zijn verantwoordelijk voor de meeste uitgaven in de zorg. De beschikbare middelen in de gezondheidszorg zijn beperkt, en daarom is het noodzakelijk dat beleidsmakers interventies vergoeden die de gezondheidswinst maximaliseren tegen acceptabele kosten. 'Health Technology Assessment' (HTA) is een onderzoeksgebied dat zich bezighoudt met het ondersteunen van beleidsmakers bij het prioriteren en vergoeden van interventies in de gezondheidszorg. HTA-onderzoek kan de verhouding tussen de effectiviteit en de kosten van nieuwe interventies en de effectiviteit en kosten van bestaande interventies in kaart brengen.

Dit proefschrift verkent de toepassing van HTA op het gebied van letsel, geestelijke gezondheidszorg, en preventie met als doel om de kosteneffectiviteit van interventies te onderzoeken en om het meten van gezondheidsgerelateerde kwaliteit van leven binnen deze gebieden te verbeteren.

We hebben ons gericht op drie belangrijke aspecten van HTA-onderzoek. In deel I hebben we ons gericht op het systematisch verzamelen van het huidige bewijs rondom de kosteneffectiviteit van interventies en het beoordelen van de methodologische kwaliteit van de gevonden studies. In deel II hebben we beschikbare gegevens over de epidemiologie, kosten en effectiviteit van preventieve interventies gecombineerd om de kosteneffectiviteit te modelleren en om de belangrijkste drijvers van de kosteneffectiviteit en onzekerheid rondom de kosteneffectiviteit te identificeren. Deel III van dit proefschrift beslaat de methodologische aspecten van het meten van kwaliteit van leven bij letsel patiënten door middel van de EQ-5D-3L vragenlijst. De doelstellingen van dit proefschrift zijn als volgt:

1. Het beoordelen van de kosteneffectiviteit van preventieve interventies op het gebied van de geestelijke gezondheidszorg en letsel, en het beoordelen van de methodologische kwaliteit van de betreffende studies **(Deel I: Synthese van bewijs)**
2. Het bepalen van de kosteneffectiviteit van preventieve interventies voor paniekstoornis en subfertiliteit, en het identificeren van de belangrijkste drijvers van de kosteneffectiviteit en onzekerheid door middel van modelleertechnieken **(Deel II: Modelleren van kosteneffectiviteit)**
3. Het onderzoeken van de toegevoegde waarde van alternatieve benaderingen voor het meten van gezondheidsgerelateerde kwaliteit van leven bij letsel patiënten

door middel van de EQ-5D-3L vragenlijst **(Deel III: Gezondheidsgerelateerde kwaliteit van leven)**

Deel I: Synthese van bewijs

Dit proefschrift beschrijft twee systematische reviews van economische evaluaties van interventies in de gezondheidszorg, en één systematische review over de prevalentie van psychische stoornissen na letsel. In *hoofdstuk 2* hebben we een systematische review over economische evaluaties van interventies voor angststoornissen uitgevoerd. Er zijn 42 relevante studies geïdentificeerd. De interventies zijn onderverdeeld in farmacotherapie, psychotherapie, psychologische interventies die (deels) via internet worden gegeven (internetbehandeling), en combinatiebehandeling bestaande uit zowel farmacotherapie als psychotherapie. Internetbehandeling bleek kosteneffectief ten opzichte van de vergelijkende behandelingen. Ondanks dat de vergelijkbaarheid van de studies beperkt werd door heterogeniteit in interventies, studie opzet, uitkomstmaten, en methodologische kwaliteit lieten de resultaten zien dat psychologische interventie meer kosteneffectief waren dan farmacotherapie. De gezondheidseconomische studie opzet en uitkomstmetingen van alle geïncludeerde studies werden voldoende bevonden, maar er was veel variatie in de kwaliteit van de individuele studies.

In *hoofdstuk 3* hebben we een systematisch literatuuronderzoek gedaan naar economische evaluaties van valpreventie programma's voor ouderen. Eenendertig studies werden geïncludeerd. We hebben een maatschappelijke 'willingness-to-pay' waarde van $50.000 per 'quality-adjusted life year' (QALY) toegepast, wat betekent dat we hebben aangenomen dat de maatschappij bereid is om $50.000 per gezond levensjaar te betalen. Huisaanpassingen waren het meest kosteneffectief voor zelfstandig wonende ouderen, en medicatiebeoordelingen waren het meest kosteneffectief voor niet zelfstandig wonende ouderen. De resultaten voor gemengde populaties waren echter inconsistent. Bij een toename van de maatschappelijke 'willingness-to-pay' ($100.000 per QALY) waren beweegprogramma's, huisaanpassingen, en medicatiebeoordelingen allemaal kosteneffectief. De kosteneffectiviteit van multifactoriële programma's en overige programma's was minder gunstig. De gemiddelde studiekwaliteit was goed (84%) en er was geen significante correlatie tussen de kwaliteitsscores en de gerapporteerde incrementele kosteneffectiviteitsratio's (ICERs).

Onze doelstelling in *hoofdstuk 4* was het geven van een overzicht van de gepubliceerde literatuur over de prevalentie en prevalentietrajecten van posttraumatische stress stoornis (PTSS), acute stress stoornis (ASS), en depressie na geweldsgerelateerd letsel dat is behandeld op de spoedeisende hulp. Bovendien hebben we de kwaliteit van de studies beoordeeld. We hebben een systematisch literatuuronderzoek uitgevoerd, wat zestien relevante studies opleverde. Vijftien studies rapporteerden de prevalentie van PTSS na geweldsgerelateerd letsel, vijf studies rapporteerden de prevalentie van ASS, en vijf studies rapporteerden de prevalentie van depressie. Er was veel variatie in de gerapporteerde prevalentieschattingen van PTSS. De prevalenties varieerden tussen de 2% (6 maanden na letsel gemeten) en 66% (<1 maand na letsel gemeten). Longitudinale studies lieten zien dat dat de PTSS-prevalentie afnam over de tijd, maar na twaalf maanden nam de prevalentie weer toe. De ASS-prevalentie varieerde tussen de 12% en 41% (beide gemeten binnen de eerste week na letsel). De gerapporteerde depressie prevalentieschattingen varieerden tussen de 5% en 41% (beide <1 maand na letsel gemeten). Duidelijke prevalentietrajecten konden niet worden geïdentificeerd. Heterogeniteit door het gebruik van verschillende diagnostische instrumenten beperkte de vergelijkbaarheid van de gerapporteerde prevalentieschattingen, en er was sprake van bias door een lage respons en studie uitval in de geïncludeerde studies.

Deel II: Modelleren van kosteneffectiviteit

Hoofdstuk 5 beschrijft een kosteneffectiviteitsmodel van een op cognitieve gedragstherapie gebaseerde vroege interventie voor 'subthreshold' paniekstoornis. Bij 'subthreshold' paniekstoornis is er sprake van paniekklachten, maar wordt er niet voldaan aan de diagnostische criteria van paniekstoornis. Het model was ontworpen om de kosteneffectiviteit van het toevoegen van de vroege interventie aan de standaard zorg voor paniekstoornis in Nederland te onderzoeken. Het toevoegen van de vroege interventie aan de huidige zorg voor paniekstoornis resulteerde in gemiddeld 3,30 QALYs en €59.355 per patiënt na vijf jaar. De huidige zorg alleen resulteerde in 3,28 QALYs en €59.634 per patiënt. De ICER vanuit het maatschappelijke perspectief resulteerde in €-23.127 per QALY, wat betekent dat de vroege interventie potentieel kostenbesparend is. De sensitiviteitsanalyses lieten zien dat de resultaten robuust waren. De doelstelling in *hoofdstuk 6* was het identificeren van onderzoeksprioriteiten met betrekking tot de kosteneffectiviteit van de vroege interventie door middel van een 'value of information' (VOI) analyse. Bovendien hebben we onderzocht in welke mate het gekozen perspectief

van invloed is op de prioriteitenstelling. De vroege interventie was kostenbesparend vanuit het maatschappelijk perspectief, maar niet vanuit het gezondheidszorgperspectief. Vanuit het gezondheidszorgperspectief resulteerde de ICER in ongeveer €17.000 per QALY. Verder onderzoek om de onzekerheid rondom de parameters in het model te elimineren werd gewaardeerd op €130 miljoen vanuit het gezondheidszorgperspectief en €30 miljoen vanuit het maatschappelijke perspectief voor de gehele populatie. Onze bevindingen lieten zien dat de prioriteitenstelling voor vervolgonderzoek vanuit de verschillende perspectieven sterk verschilde. Een ander kosteneffectiviteitsmodel was ontwikkeld voor het beoordelen van de kosteneffectiviteit van een online coaching programma Slimmer Zwanger, een preventieve interventie die ontwikkeld is om subfertiele vrouwen te stimuleren om een gezonde voedings- en leefstijl aan te nemen voorafgaand aan een in-vitrofertilisatie (IVF) behandeling in het Erasmus MC (hoofdstuk 7). De analyse was uitgevoerd vanuit het maatschappelijke perspectief, en het aantal zwangerschappen en de maatschappelijke kosten werden gebruikt als modeluitkomsten. Bij de studiepopulatie van ongeveer 800 subfertiele vrouwen resulteerde Slimmer Zwanger in 86 additionele zwangerschappen en bespaarde €270 duizend ten opzichte van de huidige zorg na twee 'single embryotransfer' IVF-cycli. De incrementele kosteneffectiviteitsratio resulteerde in €-3.050 per additionele zwangerschap, wat aangaf dat de interventie kostenbesparend was. De grootste kostenbesparingen werden veroorzaakt door de IVF zorgkosten die voorkomen konden worden. De sensitiviteitsanalyses lieten zien dat de onzekerheid rondom de kosteneffectiviteitsschatting toenam bij een lagere effectiviteit van de interventie.

Deel III: Gezondheidsgerelateerde kwaliteit van leven

De waarde van het toevoegen van een cognitief domein aan de EQ-5D-3L vragenlijst voor het meten van gezondheidsgerelateerde kwaliteit van leven was onderzocht in een cohort van letsel patiënten (hoofdstuk 8). Onze bevindingen lieten zien dat extreme cognitieve problemen in combinatie met geen problemen op de andere domeinen weinig voorkwamen, maar dat ernstige problemen op de andere domeinen in combinatie met weinig cognitieve problemen wel vaak voorkwamen. De EQ-VAS nam significant af bij cognitieve problemen. Bovendien lieten univariate regressieanalyses zien dat alle EQ-5D domeinen inclusief het cognitieve domein geassocieerd waren met de EQ-VAS. Verkennende analyses lieten zien dat het gebruik van iedere set van vijf van de zes

EQ-5D en cognitie domeinen in een bijna identieke verklaarde variantie resulteerde en dat het toevoegen van het overgebleven zesde domein in een vergelijkbare additionele impact resulteerde.

Discussie

Het doel van dit proefschrift was het verkennen van de toepassing van HTA op het gebied van letsel, geestelijke gezondheidszorg, en preventie met als doel om de kosteneffectiviteit van interventies te onderzoeken en om het meten van gezondheids-gerelateerde kwaliteit van leven binnen deze gebieden te verbeteren.

We hebben laten zien het combineren van beschikbaar gezondheids-economisch bewijs van individuele studies kan helpen bij het identificeren van de meest kosteneffectieve interventies voor angststoornissen en valpreventie bij ouderen. De variatie in methodologische kwaliteit tussen de gepubliceerde economische evaluaties was groot binnen deze gebieden, wat de vergelijkbaarheid van de resultaten belemmerde. We hebben hiermee het belang aangetoond van het van ontwerpen, uitvoeren, en rapporteren van kosteneffectiviteitsstudies conform de huidige gezondheids-economische richtlijnen om de kwaliteit van het gezondheids-economische bewijs en de vergelijkbaarheid tussen studies te versterken.
In dit proefschrift hebben we gezondheids-economische modelleertechnieken gebruikt om de kosteneffectiviteit van interventies te berekenen en om de onzekerheid rond de kosteneffectiviteitsschattingen te waarderen. Het financiële risico dat gepaard gaat met het kiezen voor een interventie met de huidige beslisonzekerheid werd gewaardeerd met VOI, en deze waarde bleek sterk af te hangen van het gekozen perspectief. Ons onderzoek benadrukt dat het kiezen van het gezondheids-economische perspectief van economische evaluaties (gezondheidszorgperspectief en het maatschappelijke perspectief) bedachtzaam gekozen dient te worden omdat de kosteneffectiviteit gunstiger kan zijn wanneer de kosten buiten de gezondheidszorg worden meegenomen. Dit geldt vooral voor preventieve interventies. Het is echter een uitdaging om alle relevante data te modelleren omdat ze lastig vaak niet beschikbaar zijn, met name lange termijn data. Daarom wordt aangeraden dat het uitvoeren van gezamenlijke modelleerprojecten prioriteit moet krijgen in onderzoek. Toegankelijke basismodellen met hoge kwaliteit en lange termijn data zouden ontwikkeld moeten worden. Deze modellen kunnen worden uitgebreid en

aangepast zodat specifieke onderzoeksvragen beantwoord kunnen worden.

Het toevoegen van bolt-ons aan de EQ-5D vragenlijst kan ervoor zorgen dat de gunstige effecten van interventies adequaat gereflecteerd worden in QALY schattingen bij economische evaluaties. We hebben aangetoond dat de verklaarde variantie toenam wanneer het cognitieve domein werd toegevoegd aan de EQ-5D-3L bij letsel patiënten. Er is echter meer onderzoek nodig naar de cognitie bolt-on en andere bolt-ons om het toevoegen van het cognitieve domein te rechtvaardigen bij het meten van de HRQOL van deze patiënten. De EQ-5D heeft zijn limitaties, en het uitsluitend gebruik maken van bestaande meetinstrumenten is mogelijk geen goede manier om interventies te evalueren op het gebied van letsel, maar ook in het algemeen. Meer onderzoek naar HRQOL metingen is nodig aangezien problemen met responsiviteit een directe invloed kunnen hebben op kosteneffectiviteitsschattingen en vergoedingsbesluiten.

ABBREVIATIONS LIST

Abbreviations list

ASD	Acute stress disorder
CBA	Cost-benefit analysis
CBT	Cognitive behavioral therapy
CEA	Cost-effectiveness analysis
CEAC	Cost-effectiveness acceptability curve
CHEC	Consensus on Health Economic Criteria
CUA	Cost-utility analysis
DISS	Dutch Injury Surveillance System
DSM IV/V	Diagnostic and Statistical Manual of Mental Disorders $4^{th}/5^{th}$ edition
ED	Emergency department
EQ-VAS	EQ-5D visual analogue scale
EVPI	Expected value of perfect information
EVPPI	Expected value of partially perfect information
GAD	Generalized anxiety disorder
HRQOL	Health-related quality of life
HTA	Health Technology Assessment
ICER	Incremental cost-effectiveness ratio
IVF	In vitro fertilization
MBEE	Model-based economic evaluation
NMB	Net monetary benefit
OCD	Obsessive compulsive disorder
PD	Panic disorder
PTSS	Post-traumatic stress disorder
QALY	Quality-adjusted life year
QUIPS	Quality in Prognosis Studies
SSRI	Selective serotonin inhibitor
SP	'Smarter Pregnancy' intervention
STHPD	Subthreshold panic disorder
TBEE	Trial-based economic evaluation
TCA	Tricyclic antidepressant
VOI	Value of information
WTP	Willingness-to-pay

LIST OF PUBLICATIONS

List of publications

Ophuis RH, Lokkerbol J, Haagsma JA, Hiligsmann M, Evers S, Polinder S. Value of information analysis of an early intervention for subthreshold panic disorder: Healthcare versus societal perspective. PloS one. 2018;13(11):e0205876.

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DANKWOORD

Dankwoord

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Robbin

CURRICULUM VITAE

Curriculum Vitae

Robbin Hendrikus Ophuis was born on November 25th in Oldenzaal, the Netherlands. After the completion of his pre-university education at the Twents Carmel College in Oldenzaal in 2010 he started studying Health Sciences with special focus on mental healthcare at Maastricht University. After obtaining a bachelor's degree in 2014, he started the Health Technology Assessment track of Research Master in Health Sciences in Maastricht. As part of the Master's program he worked at the Netherlands Institute for Mental Health and Addiction (Trimbos instituut) in Utrecht where he performed research on the cost-effectiveness of interventions for anxiety disorders. In 2016 he was appointed as a PhD candidate at the Department of Public Health of the Erasmus University Medical Center in Rotterdam, which resulted in this thesis. Robbin is currently working as a pharmaco-economic advisor at the National Health Care Institute (Zorginstituut Nederland) in Diemen, the Netherlands.

PHD PORTFOLIO

PhD portfolio

Name PhD student: Robbin Ophuis **Promotor:** Prof.dr.ir. A. Burdorf

Department: Public Health **Copromotors:** Dr. S. Polinder and Dr. J.A. Haagsma

General academic courses	**Year**	**ECTS**
Biomedical English writing and communication	2018	1
Scientific integrity	2017	0,5
Netherlands Institute for Health Sciences (NIHES) courses		
Methods of Health Services Research	2017	1,1
From Problem to Solution in Public Health	2017	0,6
Other courses		
Coping with work related stress, Erasmus MC	2018	1,5
Basiscursus Regelgeving en Organisatie voor Klinisch onderzoekers (BROK)	2017	1,5
Oral Presentations		
Presentations at the Department of Public Health, Erasmus MC	2017-2018	1
Society for Medical Decision Making (SMDM), Leiden, the Netherlands	2018	2
Trimbos institute, Utrecht, the Netherlands	2016	1,5
Conferences		
Society for Medical Decision Making (SMDM), Leiden, the Netherlands	2018	2,5
Lowlands Health Economic Study Group (LolaHESG), Rotterdam, the Netherlands	2017	1,5
Lowlands Health Economic Study Group (LolaHESG), Ghent, Belgium	2016	1,5
Seminars and symposia		
Seminars at the Department of Public Health, Erasmus MC	2017-2018	2,5
Career Day, Erasmus MC	2017	0,2
Time management, Erasmus MC	2016	0,1
VGE/VGR symposium 'Het Recht op Zorg'	2017	0,5
Workshop handling personal data	2017	0,1
Fall symposium, Academic Medical Center, Amsterdam, the Netherlands (2x)	2017-2018	0,4
Review activities		
Journal of Affective Disorders	2017	0,3
BMC Psychiatry	2017	0,3
Teaching		
Supervising community project	2018	1,5
Lecturing 'Hoe houden we de zorg betaalbaar'	2018	3
Correction of the 'GENBA2A120 - Oncologie (REG)' exam	2017	0,5
Correction of the 'GENBA3C - Arts en volksgezondheid (REG)' exam	2017	0,5
Correction of the 'GENBA3C - Arts en volksgezondheid (HER)' exam	2017	0,5
Other		
Mentoring program, Erasmus MC	2017-2018	0,4