Technische Universität München

TUM School of Medicine and Health

Are Internet- and Mobile-Based Interventions in Mental Health a Good Value for Money?

Efficacy and Cost-Effectiveness of Internet- and Mobile-based Interventions in Prevention and Treatment of Mental Disorders.

Fanny Kählke, M. Ed.

Vollständiger Abdruck der von der
TUM School of Medicine and Health der Technischen Universität München
zur Erlangung einer Doktorin der Philosophie (Dr. phil.)
genehmigten Dissertation.

Vorsitz:	Prof. Dr. Manuel Spitschan
Prüfer*innen der Dissertation:	1. Jun.-Prof. Dr. Claudia Buntrock
	2. Prof. Dr. Michael Laxy
	3. Prof. Dr. Jan Philipp Klein

Die Dissertation wurde am 11.11.2022 bei der Technischen Universität München eingereicht und durch die Fakultät für Sport- und Gesundheitswissenschaften am 12.07.2023 angenommen.

Never give up on a dream just because of the time it will take to accomplish it.
The time will pass anyway.

– Earl Nightingale –

Acknowledgements

This thesis project started when I applied for my PhD position with the desire to have a positive impact on people's health, so that they can live a fulfilled life. The project itself proved to be challenging and has accompanied me through various stages of my personal life. During this time, I started working at the Friedrich-Alexander Universität Erlangen-Nürnberg (FAU) in Erlangen and later moved to Munich to start a family and work at the Technische Universität München. The completion of my PhD thesis would not have been possible without the help and support of numerous people, who I would like to thank in the following lines.

First, my thanks go to my beloved family. My husband Andreas who always encouraged me to pursue my dream of promoting people's health. His irrepressible trust in my talents helped me to begin, persevere and finish my PhD. Without him, this work may not exist. In this regard I also thank my children Clara and Theodor for allowing me time away from them to write this thesis.

Second, I would like to thank my supervisor David D. Ebert, who gave me the chance to work in the StudiCare project. He was confident in my potential early on and provided me with the room and resources to grow beyond myself.

Third, I'd like to thank my dear college Claudia Buntrock for the endless hours we spent discussing cost-effectiveness, our shared pragmatic nature, the time spent in our shared workplace, and all the elaborate comments that further improved my research and served as a role model for good research practice.

Fourth, I'd like to thank Ann-Marie Küchler. She made working for in my project StudiCare very productive and pleasant. I hope that we will work together in the future. In this regard I likewise thank the whole StudiCare Team: Marvin Franke, Karina Bernstein, and Mathias Harrer.

In addition, I want to thank my colleagues at the chair of Clinical Psychology and Psychotherapy at the FAU and at the Professorship of Psychology and Digital Mental Health Care at the TUM that cheered me up and helped me navigate through difficult situations and challenges. I can look back upon a wonderful time together that we also spent traveling to many national and international conferences. Managing a randomized controlled trial and cleaning data is very time-consuming and it would not have been possible without the support of my former master's students Julia Burger und Mirjam Schulz who both did an outstanding job and contributed to the progress of this project through their organizational talent and their brilliant ideas. A further thanks goes to Avery Veldhouse for proofreading the thesis.

Table of Contents

List of Abbreviations i

Abstract iii

1. General Introduction 1

1.1. The (economic) burden of mental disorders and symptoms 1

1.2. The burden of social anxiety disorder 4

1.3. The burden of chronic stress 5

1.4. Treatment gaps in mental healthcare 7

1.5. Internet- and mobile-based interventions in mental health 8

1.5.1 Efficacy of IMIs 9

1.5.2 The cost-effectiveness of IMIs 11

2. Methodology 14

2.1 Study 1: Efficacy and Cost-effectiveness of an IMI on SAD 14

2.2 Study 2: Cost-effectiveness of an iSMI for employees 16

2.3 Study 3: A Systematic Review on Cost -Effectiveness in IMIs 18

3. Publications and Submissions 21

3.1 Article 1: Study protocol – IMI for Students with SAD 22

3.2 Article 2: Efficacy of an IMI for Students with SAD 36

3.3. Article 3: Long-term efficacy and cost-effectiveness of an IMI for SAD 50

3.4 Article 4: Cost-Effectiveness of an iSMI from Employer's Perspective 73

3.5 Article 5: Cost-Effectiveness of an iSMI from Societal Perspective 88

3.6 Article 6: Systematic Review of Cost-Effectiveness in IMIs 105

4. General Discussion 133

4.1 Aims of this thesis 133

4.2 Main findings 133

4.3 Comparison with previous research 134

4.3.1 Study 1 134

4.3.2 Study 2 136

4.3.3 Study 3 137

4.4 Limitations 138
4.5 Clinical Implications 140

4.5.1 Study 1 140
4.5.2 Study 2 142
4.5.3 Study 3 144

4.6 Challenges and directions for future research 145

4.6.1 Self-help IMIs in routine care 145
4.6.2 Adherence in unguided interventions 147
4.6.3 Precision medicine in the treatment of SAD 148
4.6.4 Recommendations for future (clinical) research 149
4.6.5 Challenges in trial-based health economic evaluation 150
4.6.6 The German reluctance to use health economic evaluations 150
4.6.7 Recommendations for future research on health economic evaluations 153

4.7 Conclusion 155

5. References 156
6. Appendix iv

List of Publications iv
About the Author vii

List of Abbreviations

AC	Attention control
ACT	Acceptance commitment therapy
AFG	Adherence-focused guidance
ANCOVA	Analysis of covariance
AQoL-8D	Assessment of Quality of Life
AUC	Area under curve
CBA	Cost-benefit analysis
CBM	Cognitive bias modification
CBT	Cognitive behavioral therapy
CEA	Cost-effectiveness analysis
CEAC	Cost-effectiveness acceptability curve
CENTRAL	Cochrane Central Register of Controlled Trials
CHEC	Consensus on Health Economic Criteria
CHEERS	Consolidated Health Economic Evaluation Reporting Standards
CI	Confidence interval
CMA	Cost-minimization analysis
COVID-19	Coronavirus Disease 2019
CUA	Cost-utility analysis
DALYS	Disability-adjusted life-years
DiGA	Digital health applications
DSM-5	Diagnostic and Statistical Manual of Mental Disorders, Version 5
EF	Efficiency frontier
EFPA	E-Health Taskforce of the European Federation of Psychologists' Association
EQ-5D	EuroQol Quality of Life 5 Dimensions
F2F	Face to face
FPE	Fear of positive social evaluation
FU	Follow-up
GAD	Generalized anxiety disorder
GKV-SV	National Association of Statutory Health Insurance Funds
HTA	Health Technology Assessment
iCBT	Internet-supported cognitive behavioral therapy
IG	Intervention group
IMI	Internet- and mobile-based interventions
IQWiG	Institute for Quality and Efficiency in Health Care
iSMI	Internet-based stress-management intervention
ISPOR	International Society for Pharmacoeconomics and Outcomes Research
ITT	Intention-to-treat
MDD	Major depressive disorder
NHS	National Health Service
NICE	National Institute for Health and Clinical Excellence
OLS	Ordinary least squares regression

PD	Panic disorder
PSS-10	Perceived Stress Scale (10 items)
PTSD	Post-traumatic stress disorder
QALY	Quality-adjusted life years
RCT	Randomized controlled trial
RoB	Assessing risk of bias
ROI	Return of investment
SAD	Social anxiety disorder
SCID-I	Structured Clinical Interview for DSM-IV Axis I Disorders
SGB V	German Social Code Book V [Sozialgesetzbuch]
SH	Self-help
SHI	Statutory health insurance
SIAS	Social Interaction Anxiety Scale
SMD	Standardized mean difference
SMI	Stress management interventions
SNRI	Serotonin-norepinephrine reuptake inhibitors
SPS	Social Phobia Scale
SSRI	Selective serotonin reuptake inhibitors
SURE	Seemingly unrelated regression equations model
TAU	Treatment as usual
TiC-P	Trimbos and iMTA questionnaire for costs associated with psychiatric illness
VAT	Value added tax
VRE	Virtual reality exposure
WHO	World Health Organization
WLC	Waitlist control group
WMH-ICS	World Mental Health International College Student
WTP	Willingness to pay

Abstract

Mental disorders have been on the rise for decades. Today they have become a major global public health issue. Economic costs like direct costs for e.g., medication or physician visits and indirect costs such as productivity losses due to work absence are enormous. Even highly developed healthcare systems are struggling with a tremendous treatment gap leading to the majority of people in need remaining untreated. Internet and mobile-based interventions (IMIs) offer low-threshold treatments of mental disorders that overcome existing treatment barriers. Evidence for such treatments' efficacy is increasing. Yet, for pure self-help interventions and under-researched disorders, cost-effectiveness evaluations are scarce. This thesis aims to provide further insight into the effects and costs associated with IMIs, particularly via a study of (1) the efficacy and cost-effectiveness of an unguided IMI for social anxiety disorder (SAD) in students, a study of (2) the cost-effectiveness of an internet-based stress-management intervention (iSMI) in employees, and a study of the (3) cost-effectiveness across mental disorders with different guidance, cost perspectives and health economic evaluations.

Study One evaluates an unguided self-help intervention targeting SAD in students compared to a waitlist control group (WLC). The rationale, design, outcomes, and methods used are described in a study protocol (Article 1). The treatment efficacy based on primary outcomes for SAD, secondary outcomes (e.g., depression, anxiety), and adverse effects are reported in Article 2. Finally, Article 3 presents the long-term efficacy and cost-effectiveness of the IMI from a healthcare and a societal perspective.

Study Two analyzes the cost-effectiveness of an occupational iSMI for workplace employees with elevated stress levels compared to a WLC from an employer's (Article 4) and a societal perspective (Article 5).

Study Three is a systematic review of literature on the cost-effectiveness of IMIs for the prevention and treatment of common mental health problems (Article 6). In total, 35 randomized controlled trials were identified for various mental disorders. Most studies (n=21) were conducted from the societal perspective.

Overall, the studies in this thesis provide evidence that (1), pure self-help interventions for students SAD are both highly efficacious and cost-effective at post assessment and 6-month follow-up (FU), (2) an iSMI for employees shows a high probability of cost-effectiveness for employer's and societal perspective at 6 months FU, and (3) guided internet-based interventions targeting depression and anxiety disorders are cost-effective when compared to various control conditions. More evidence on cost-effectiveness in needed, including longer time horizons, under-researched disorders, and self-help (preventive) interventions.

1. General Introduction

*"*Good mental health and well-being are essential for all of us to lead fulfilling lives, to realize our full potential, to participate productively in our communities, and to demonstrate resilience in the face of stress and adversity[1]*."* In 2021 the World Health Organization (WHO) updated its comprehensive Mental Health Action Plan through the year 2030, focusing on the promotion of mental health and well-being and the prevention of mental disorders over the life-course, and offering universal coverage of mental health services around the globe. This action plan is founded upon the high prevalence and incidence of mental disorders, excessive barriers to healthcare utilization, and the enormous costs of mental disorders associated with disability that together lead to a high global burden of mental disorders and symptoms.

1.1. The (economic) burden of mental disorders and symptoms

Mental disorders are frequent and persistent and are a concern to the global public mental health. Worldwide, mental disorders have been highly prevalent over the past three decades and thus are the premier public health challenge of the 21st century[2]. They, alongside other non-communicable diseases, are a growing threat to the individual, the society, and the healthcare system(s). Thus, mental illness is seen as the leading cause of disability in many Western countries.

Mental and addictive disorders account for 7% of the global burden of disease measured in DALYS (disability-adjusted life-years) and engender 19% of all years lived with disability. In 2016, almost one in every six people on the planet was affected (16.6%, 1 billion people) by mental and addictive disorders[3]. The 2019 Global Burden of Disease Study compared the prevalence of the 12 most common mental disorders from 1990 to 2019 and showed that mental disorders remain one of the leading causes of burden across the world[2]. Western Europe has a higher prevalence of mental disorders compared with other regions, with anxiety and depressive disorders accounting for more than 60% (9,477 persons) of age-standardized prevalence per 100 000 persons.

Over the span of one year, about one out of ten (10.4%) individuals will suffer from depression[4], whereby more than one out of five (22.2%) will be directly affected by an anxiety disorder with specific phobias (12.1%) and social phobia (7.1%) exhibiting the highest prevalences[5]. Over the course of an individual's life this prevalence increases, doubling to one out of

every five (20.6%) individuals experiencing depression at least once, whereby one third of individuals (33.7%, including SAD: 13%, specific phobia: 13.8%) are directly affected by an anxiety disorder[4,5].

Mental disorders are not only associated with a high disease burden but also with a high degree of suffering for those affected resulting in a low quality of life[6] and increased risk of mortality[7]. Mental disorders are risk factors for the development of other psychological disorders. This risk of comorbidity is particularly high for linked mental disorder types and stays elevated for at least 15 years after onset[8]. Physical conditions such as cardiovascular disease, hypertension, diabetes mellitus, metabolic disorders and respiratory disorders also seem to be associated with mental disorders[9]. The characteristics of this relationship is still unclear. It is assumed that lifestyle factors and inadequate treatment play a crucial role. As an example, risk for depression is greater in people with diabetes and vice versa. This relationship is complex and may be explained through the combination of various biological mechanisms. Known risk factors for both disorders are low birth weight, lifestyle, obesity, and adverse childhood events[10].

The prevalence and incidence of mental disorders are also influenced by other public health emergencies. The COVID-19 (Coronavirus Disease 2019) pandemic negatively influenced determinants of mental health on the individual, social, and societal level. As an example, lockdowns in response to the public health emergency strained living circumstances, interpersonal relationships, and the social support system. Globally, infection rates and mobility restrictions correlated to an elevated prevalence of major depressive and anxiety disorders. In total, more females than males and younger than older age groups were affected, leading to an increased number of major depressive disorder (MDD, 27.6%) and anxiety disorder (25.6%) diagnoses[11]. A high prevalence of stress (29.6%), anxiety (31.9%) and depression (33.7%) was observed in the general population[12]. In particular, people with low socio-economic status and higher count of stressors showed a greater risk for depressive symptoms[13]. Nevertheless, a meta-analysis of longitudinal studies revealed that the symptom increase after the initial COVID-19 outbreak declined to a pre-pandemic level within a couple of months[14]. This can be explained by negative life events being followed by resilience or recovery for most people[15].

Mental disorders are widespread and associated with tremendous economic costs to the individual and to society. Employees suffering from mental disorders often feel sick and thus are less efficient at (presenteeism) or more frequently absent from work (absenteeism). This limited ability to participate in the labor market can result in the reduction or loss of income and early retirement[16]. Therefore, general workforce productivity losses and reduced

income taxes as well as direct treatment costs of mental disorders lead to substantial national and societal costs[16].

The human capital approach is commonly applied to calculate the economic costs of mental disorders, differentiating between direct and indirect costs. The "visible" direct costs refer to services in healthcare systems, such as diagnosis, treatment, and care, including medical costs (e.g., medication, physician contacts, hospitalization), and non-medical costs (e.g., transportation). The "invisible" indirect costs refer to productivity and income losses due to disability or premature death[17]. Intangible costs are neither quantified in monetary terms nor captured by the human capital approach. These include pain and suffering resulting from negative mood, a patient's stress concerning the inability to pay for healthcare services, or the patient's family's stress resulting from e.g. communication disabilities due to the disease[18].

In the European Union costs attributable to mental disorders, tallying €798 billion in 2010, are expected to double by 2030[19]. The World Economic Forum expects global costs associated with mental disorders to likewise more than double—from US$2.5 trillion to US$6 trillion—in the same time span due to an increased demand of services and associated treatment costs[20]. Of these costs, indirect costs are predicted to be twice as high as direct medical cost related to service use. Ergo, mental disorders cause comparatively lower direct costs to the healthcare system when juxtaposed with the high indirect costs associated with productivity losses and reduced economic growth. This is particularly true for mental disorders in contrast to other disease groups and a reason for why they account for more costs than somatic disorders. Their costs are expected to increase in the next 15 years under the assumption that more comprehensive analytic approaches for cost estimation will be deployed[17].

The implementation of evidence-based and cost-effective treatments as well as preventive strategies can reduce costs. Scaling up treatment coverage could have a positive effect on health, economic and social aspects[21]. Positive health effects occur when treatment effects lead to recovery or remission, hence more healthy life-years lived. Economic effects manifest as a result of decreased healthcare costs due to the successful treatment of mental disorders or the restored ability to participate in the labour market. Social effects refer to individuals or households that can pursue their leisure activities and participate in communities again.

The global return on investment of standard treatments of mental disorders over the period 2016 to 2030 has been estimated using a projected linear increase of treatment coverage under the assumption that standard treatment costs and effects lead to an increased productivity and ability to work. Thus, to adequately scale up an effective treatment coverage for depression and anxiety disorders, an estimated total of US$147 billion are needed[21]. This

investment would in turn lead to 43 million additional years of healthy life, representing a net present value of $310 billion[21]. Expanding treatment coverage can only partially close the globally observable treatment gap, as strong barriers to seeking help for those affected by mental disorders exist.

1.2. The burden of social anxiety disorder

The first study presented in this thesis sheds light on the efficacy and cost-effectiveness of a self-help intervention targeting social anxiety disorder (SAD) as an as an example for the potential of internet-based treatment of mental disorders. The following section presents the condition, its associated consequences, and its treatment options. SAD, also known as social phobia, is a prominent condition with a lifetime prevalence of 4% worldwide and 2.5% in Germany. On average, close to 90% of those affected will experience the onset of the disorder by age of 25[22]. In Germany, a regional study on young adults aged 18 to 21 years revealed a life time prevalence of 8% (95% CI[6.0, 10.5])[23].

The current Diagnostic and Statistical Manual of Mental Disorders (DSM-5, fifth edition) describes SAD in adults as (1) fear of specific social settings (e.g., first date, oral presentation), (2) fear of social rejection or display of anxiety, (3) social interactions that trigger distress and are (4) avoided or reluctantly endured, and as (5) a fear that is disproportionate to the actual situation. All listed criteria must persist for six months or longer, cause personal distress and/or impaired functioning in one or more domains (e.g., interpersonal, occupational), and must not be attributable to other causes (e.g., medical disorders, another mental disorder)[24]. The etiology of SAD is understood to be an interplay between individual (e.g., genetic, temperamental, cognitive, behavioral) and environmental factors (e.g., parental overcontrol, parental psychopathology, adverse life events)[25].

Modifiable individual risk factors for the development of SAD are cannabis use, avoidance behavior in social situation that are not dangerous, low social support, and dysfunctional attitudes[26]. Patients with SAD are also frequently affected by comorbidity leading to disease progression, elevated symptom severity, treatment resistance and reduced functioning[27]. Comorbidity such as major depression can complicate diagnosis and treatment. However, early treatment is necessary to prevent adverse consequences. SAD patients show at least one severe role impairment related to the home, work, relationship, or social life domain[22]. The presence of SAD is associated with younger age, being unmarried, having lower education and income. Both the absence of work and the reduced quantity, quality, and concentration at work

due to SAD lead to a high economic burden for society. Mental illnesses such as SAD are rated amongst the conditions with the highest annual costs based on daily estimated productivity losses, on par with chronic back pains and migraines[28]. The disease burden, costs, and role impairment highlight the need for an early and effective treatment of SAD. To date, there are several effective treatments available.

First-line treatments include psychotherapy based on cognitive behavioral therapy (CBT) that are most effective in an individual or group setting that aims at providing behavioral and cognitive strategies to alter maladaptive cognitions and behaviors. Additional pharmacotherapy such as selective serotonin reuptake inhibitors (SSRI) and serotonin-norepinephrine reuptake inhibitors (SNRI) is recommended. Online psychotherapy, virtual reality exposure (VRE), and third wave approaches of CBT (e.g., mindfulness-based therapy) are seen as innovative and useful treatment options[29]. According to a systematic review and network meta-analysis, psychological treatments vary in effect size d = -0.92 for group CBT, d = -1.19 for individual CBT, d = -0.86 for self-help with support, and d = -0.75 for self-help without support, when compared to a waitlist control condition (WLC). Compared to a placebo, only individual CBT (d = -0.56), and SSRIs and SNRIs (d = -0.44) showed greater effects[30]. Despite the existence of effective treatment options, patients with SAD are often reluctant to seek help in a face-to face (F2F) setting due to fear of stigmatization and shame. Additionally other barriers such as delayed treatment provision, a high distance to healthcare providers, and the lack of psychotherapists inhibit treatment utilization[31].

1.3. The burden of chronic stress

The second study presented in this thesis focuses on the cost-effectiveness of an internet-based stress management intervention targeting elevated stress in employees—a form of preventive intervention. The following section illustrates the role of stress as a trigger and risk factor in the development of mental disorders. Most contemporary theories take an integrative biopsychosocial approach[32] to mental disorders, describing them as an interweave of psychological, sociocultural and biological factors. These “risk” factors can elevate the risk of psychological problems. Biological (genetic disposition, brain anomalies), social (chronic stress, maladaptive upbringing) and psychological (poor skills, maladaptive cognitions) risk factors are seen as vulnerabilities or “diatheses”, that may not be sufficient to cause the development of severe psychological symptoms on their own[33]. These vulnerabilities, in combination with a trigger (e.g., stress) such as a change in hormone levels (biological), a traumatic life event

(sociocultural) or perceived loss of control (psychological) can lead to a mental disorder. This understanding of the development of a mental disorder is referred to as the Diathesis-Stress Model or Vulnerability-Stress Model. New research suggests an extension of the model by adding coping factors as an additional dimension creating an extended Vulnerability-Stress-Coping Model of Mental Disorders[34].

In practice, research shows that stress affects both mental and physical health. Acute psychological stress evokes a fight-or-flight response. Systematic evidence shows that both high and low stress reactivity have an impact on long-term health and disease[35]. Exaggerated stress reactivity increases the risk for cardiovascular disease whereas blunted stress reactivity increases the risk for adiposity, obesity, elevated depression, anxiety and post-traumatic stress symptoms and musculoskeletal pain. Furthermore, long-lasting stress and chronic psychological stress can lead to several psychological and physical impairments like depression[36], sleep disorders[37], or coronary heart disease[38].

Given the adverse effects of stress on health and its role in the etiology of mental disorders, building better coping and stress management skills is beneficial and important for promoting good mental health. Numerous stress models exist. These include more specific models, such as the effort-reward imbalance model[39] or the job-demand control model[40], as well as more generic models, such as Lazarus's transactional model[41]. Treatment approaches are similarly diverse, utilizing approaches such as mindfulness training, CBT, emotion regulation training and the development of problem-solving skills. Stress management interventions (SMI) focus on the individual through counselling or relaxation as opposed to changed working schedules and conflict management offers on the organizational level. Individual-level interventions aim to prevent stress from occurring using three different types of interventions. Primary interventions screen and select patients who might be susceptible to stress (e.g., medical examination). Secondary interventions aim to increase skills and abilities to manage stress and promote well-being (e.g., meditation, acceptance commitment therapy (ACT), mindfulness training, CBT). Tertiary interventions (e.g., counselling, disability management) focus on employees that experience chronic work ability impairing stress levels[42]. In Germany, multimodal stress management is the most common stress management concept, based on three core competencies. Instrumental competence helps to identify stressors. Mental competence creates positive attitudes and evaluations towards stress. Regenerative competence focuses on relaxing and recovering[43].

Small to moderate overall effects on mental health were already evident in a review of reviews conducted between 1990 and 2011 on SMIs at the workplace[44]. There exist various

intervention types such as cognitive-behavioral approaches, relaxation techniques, or multimodal and organization-focused interventions that target stress-related psychological problems, including job stress, burnout, mental fatigue, and adjustment disorder. Overall, evidence shows that CBT-based interventions are the most effective[45]. SMIs can be seen as preventive interventions whose application can help minimize the economic costs and psychosocial impact of elevated stress and its associated disorders. At the workplace, employers depend on their workforce's health to maintain high productivity and monetary benefits. However, in other settings, such as during early life or at the population level, the benefits of preventive interventions are smaller, indirect, and often delayed, whilst costs are incurred upfront[46]. This is one of the factors that cause a substantial gap between those in need of help and those seeking help, engendering many individuals to seek initial treatment at later stages of their disease progression[47].

1.4. Treatment gaps in mental healthcare

There exist many effective and evidence-based psychological and pharmacological treatments for mental disorders[48–51]. Nonetheless, most individuals suffering from one or more psychological disorders remain untreated. For example, treatment coverage across low, middle, and high-income counties ranges from 5% to 28% for anxiety disorders and depression[21]. In addition, health systems are commonly overburdened and unable to adequately deliver mental healthcare[52], which is mostly explained by a shortage of qualified personnel (e.g., psychotherapists, psychiatrists), poor accessibility of services, fragmentation of care, stigma-related barriers to seeking mental health care, and low treatment utilization. In Germany, only a small proportion of individuals diagnosed with a mental disorder (23.5% of women, 11.6% of men) reported any mental health service use over the past year[53]. The most common explanation for this "treatment gap" is the existence of barriers to mental healthcare use. Structural barriers (e.g., waiting times, limited availability of services, affordability, long travel distances to services) are known to decrease service utilization. Especially critical are the attitudinal barriers such as low perceived need, the wish to handle the problem on one's own, and stigma, which also prevent people affected by mental disorders and symptoms to seek help[54].

The German mental healthcare system is characterized by fragmented services provided by hospitals, office-based psychiatrists or psychologists, and outpatient care, as well as non-medical vocational, residential, and psychosocial services that are reimbursed through health insurances providers or tax-funded social services. This can hamper the implementation

and integration of innovative treatment concepts, resulting in discontinuity and low quality of care as well as insufficient patient involvement[55]. The estimated delay between the onset of mental disorders in people neglecting services in their first year after onset of the disorder and treatment utilization amounts to 6 years for anxiety and 7 years for mood disorders in Germany[53]. The latency between onset and treatment seeking amplifies the symptom severity and symptom chronification (i.e., the transition of symptoms from acute to chronic) and comorbidity associated with increased risk of mortality[56,57].

Digital innovations delivered by tools of our daily life (e.g., laptops, smartphones, tablet) are one possible way to address the healthcare treatment gap. The COVID-19 pandemic further underpinned the need for innovative treatment models, readily accessible health interventions, and scaled up mental healthcare through a reduction of F2F treatments and an increase of online and digital mental health services.

1.5. Internet- and mobile-based interventions in mental health

E-mental health is defined as "mental health services and information delivered or enhanced through the Internet and related technologies[58]." Various terms referring to the application and delivery of interventions via new technologies or the internet exist. The commonly used search engine for scientific databases "PubMed" incorporates "internet interventions" as a medical subject heading used to index articles on internet-based, web-based or online interventions. In the literature, various alternative terms and synonyms are used: digital mental health interventions[59], computerized or internet-supported cognitive behavioral therapy (iCBT[60]), and online self-help programs[61].

In this thesis the term internet and mobile-based intervention (IMIs) is used to refer to interventions characterized by four main features: (1) theory base, (2) application area, (3) human support, (4) technical implementation. First, evidence-based psychotherapeutic models and techniques (cognitive behavioral techniques, CBT, psychodynamic and mindfulness-based approaches) are used for the development and implementation of IMIs. Second, the modes of delivery include mostly interactive self-help interventions but also virtual reality, serious games, avatars, chatbots, feedback and reinforcement as well as phones and wearables. Third, human support, described as "guidance", is used to increase adherence to interventions but can be integrated to varying degrees. Communication between the therapist and patient takes place synchronously (video/chat) or asynchronously (e.g., via e-mail). Participants can often perform tasks and techniques independently, accompanied by regular feedback through

clinical psychologists, health professionals or trained lay health workers ("guided" self-help approaches). The degree of human support ranges from no guidance ("unguided" self-help IMI), to automated guidance, to support on demand (patient individually determines the level of support) or even intensive support (guided IMI). Adherence-focused guidance lowers attrition and increases engagement using different elements of support, e.g., email reminder or therapeutic feedback on request. Fourth, there are a variety of possible applications for IMIs including the prevention, promotion, treatment, relapse prevention of mental disorders, or chronic disease management. They can be used as stand-alone approaches, blended concepts (a combination of IMI and F2F treatments), stepped care (adjusting therapeutic support based on previous effects and patient characteristics), and specific treatment formats[62].

In short, IMIs represent a promising approach to extend the provision of evidence-based psychotherapeutic interventions to the general population. They can overcome common barriers of treatment utilization, fulfilling the desire of some individuals to solve problems by themselves. Their main benefits include: (1) low threshold access, (2) independence of time and location, (3) adaptability to individual needs through treatment flexibility and integration into daily life, (4) scalability and (5) anonymity of self-help interventions, and (6) the potential to empower users and increase self-efficacy[63].

1.5.1 Efficacy of IMIs

Over the last 20 years, evidence on the efficacy of IMIs for the prevention and treatment of mental disorders based on randomized controlled trials (RCT) has increased greatly. A recent narrative umbrella review of meta-analyses reports moderate to large effects of internet-delivered CBT on MDD, generalized anxiety disorder (GAD), panic disorder (PD), SAD, and post-traumatic stress disorder (PTSD) compared to studies on F2F treatments[64]. Other meta-analytic evidence found similar moderate to large effect sizes for MDD (Hedge's g = 0.64, 95% CI [0.51, 0.81]), PD (g = 1.31, 95% CI [0.85, 1.76]), SAD (g = 0.92, 95% CI [0.76, 1.08]), and GAD (g = 0.70, 95% CI [0.39, 1.01])[65]. However, effects diminished and could not be maintained after the follow-up (FU) period of 3 months or more[65]. Another study, this one only including guided IMIs, revealed a Hedge's g of 1.52 across a variety of disorders over a two year or longer FU period. Thus, despite their high heterogeneity, guided IMIs are likely to have long-term effects[66].

One study presented in this thesis provide evidence on the efficacy of (unguided) IMIs targeting SAD. In 2016, shortly before I started to recruit students with SAD for our internet

and mobile-based self-help intervention, "StudiCare soziale Ängste", a meta-analysis evaluating common technology-assisted psychological interventions in SAD was published[67]. These interventions were based on the principle of CBT, VRE, and cognitive bias modification (CBM). Evidence for their efficacy was substantial for CBT, limited for CBM, and preliminary for VRE. CBT showed large (*g* = 0.84, 95% CI [0.72, 0.97]) and medium (*g* = 0.38, 95% CI [0.13, 0.62]) controlled effect sizes compared with passive and active control condition at post assessment respectively[67].

No or very limited evidence on long-term effects was shown due to the lack of available data. Consequently, comparisons of the intervention groups yielded small or non-significant effect sizes compared to active (greater than or equal to 6 months, *g* = 0.23, 95% CI [0.04, 0.43]) or passive controls (less than or equal to 5 months, not significant). The presence of human support also influenced intervention outcomes, whereby guided iCBT exhibited higher effect sizes (passive: *g* = 0.87, active: *g* = 0.47) than unguided iCBT (passive: *g* = 0.78, active: *g* = 0.19 not significant). Eight studies compared unguided iCBT with passive controls with large differences in effect sizes (*g* = 0.28–1.47) and substantial drop-out rates[68–75]. FU data for active control conditions was limited and no FU data comparing unguided iCBT to passive control was available. This systematic review found a research gap regarding the (long-term) efficacy of unguided iCBT compared to passive control, and recommended future comparative efficacy and cost-effectiveness analyses (CEA) of guided versus unguided interventions. The study population of most studies was a general clinical population. However, we identified one iCBT with minimal guidance targeting students (N = 38) that showed large within group effect-sizes at post (*d* = 1.11–1.18) and FU (*d* = 0.93–1.47) assessments with and without in vivo group exposure therapy[76]. No other study evaluated the cost-effectiveness or the effects of an unguided self-help intervention targeting students with SAD.

The second study presented in this thesis provides evidence for the efficacy of a preventive internet-based stress management intervention targeting employees with elevated stress. In 2014, the American Psychological Association published Guidelines for the Prevention in Psychology acknowledging the effectiveness of preventive intervention on human functioning and the reduction of psychological distress[77]. Meta-analytic evidence supports the potential of IMIs in the prevention of mental disorders in generating small effects (SMD -0.35, 95% CI [-0.57, -0.12]). However, these findings are limited due to the paucity of studies on incidence rates including clinical diagnostics[78]. Based on Gordon's classification of disease prevention, prevention is categorized as being universal (targeting the entire population), selective (targeting subgroups of the population at risk for a disorder) or indicated (targeting individuals

showing early subclinical signs of a disorder)[79]. In the short term, IMIs based on universal, selective, and indicated prevention of anxiety and depression yield small but positive effects on symptom reduction. A recent scoping review of mental health interventions in youth with subclinical symptoms showed general effectiveness in reducing depressive symptoms, anxiety and stress, usability, and acceptability of online indicated preventive interventions[80]. The most observed treatment approach was based on CBT (n = 12, Cohen's *d* = 0.36–1.25*),* followed by CBT combined with other approaches (n = 5, *d* = -0.17–0.99) as well as ACT (n = 3, *d* = 0.62–0.78).

A systematic review and meta-analysis on web- and computer-based interventions for stress showed a medium effect size (*d* = 0.43, 95% CI [0.31, 0.54]) and small significant effects on depression (*d* = 34) and anxiety (*d* = 0.32). Once again, guided IMIs were found to be more effective than their unguided (*d* = 0.33) counterparts. CBT (*d* = 0.40) and third wave CBT (*d* = 0.53) showed small to moderate effects. Additionally, initial evidence has revealed long-term effects of stress-management interventions up to 6 months[81].

1.5.2 The cost-effectiveness of IMIs

The benefits of an intervention, in addition to the array of benefits for health and well-being, can also be assessed using economic metrics. For example, intervention costs are relevant when deciding for or against the intervention's application. Health economic evaluations assess economic aspects of an intervention. They are a multi-step process that relies on systematic considerations to make informed decisions on how to best allocate resources. First, a systematic analysis of available treatments (existing or usual care) must be conducted to assess whether or not to introduce or reject a new program. Second, a specific analytic perspective (e.g., patient, healthcare, societal) must be taken that includes different cost categories. Third, the quantification and comparison of inputs and outputs related to opportunity costs (i.e., referring to the possible gains of the next-best program that has been forgone by employing the resources for the first program) must be performed. Fourth, a possible treatment alternatives including their effects and benefits must be examined systematically to help decision-making[82].

A comprehensive assessment of benefits and harms of a treatment can be executed as a Health Technology Assessment (HTA), that includes economic considerations (e.g., cost-effectiveness analyses). The HTA is the systematic evaluation of medical procedures and technologies for population-level healthcare and consists of two different evidence phases. In the first phase, researchers collect evidence based on RCTs, cases studies, and observational studies. In the second phase, evidence is processed using modelling studies to estimate the costs and

effects in circumstances that could not or can never be observed in treatment trials, for instance due to ethical or resource concerns[83].

The latest review on the evidence and various aspects of internet- and mobile-based psychological interventions by the E-Health Taskforce of the European Federation of Psychologists' Association (EFPA) did not include cost-effectiveness[63]. Cost-effectiveness was excluded because IMIs are assumed to reduce costs of psychotherapy, and thus are cost-effective compared to other treatment options. Actually, evidence regarding their cost-effectiveness is scarce despite over 100 RCTs evaluating the efficacy of IMIs published in 2020 alone. Prior to 2016, before the studies presented in this thesis had been conducted, evidence on the health economic effects of IMIs was very limited. A 2014 review on the efficacy and the cost-effectiveness of internet-delivered psychological treatments for mood and anxiety disorders could develop no conclusion on their cost-effectiveness due to the small number of health economic evaluations and high risk of bias of these studies[84]. In 2015, a systematic review on economic evaluations of IMIs targeting mental health identified 16 articles relating to a variety of mental disorders including anxiety (n = 6), depression (n = 4), substance use (smoking cessation n = 3, alcohol n = 2), and suicide prevention (n = 1). Most studies offered guidance and utilized a societal perspective, demonstrated promising probabilities of cost-effectiveness compared to various control groups (e.g., waitlist, treatment as usual (TAU), group CBT, unguided iCBT). Three out of only six unguided interventions targeting suicide prevention, depression, and smoking cessation showed cost-effective results compared with TAU or attention control (AC), but less favorable effects per quality-adjusted life year (QALY) gained[85]. Since I began conducting the studies presented in this review, two more reviews have been published. The first review examined psychological, pharmacological, and combined interventions for anxiety disorders(N = 42)[86]. The authors found iCBT (n = 7) to be cost-effective compared with group CBT and inactive treatment, and posited that psychological interventions are more cost-effective than pharmacotherapy. The second review identified 12 IMIs for the treatment and prevention of depression (guided n = 9, unguided n = 2, both n = 1) and found that guided IMIs are likely to be cost-effective[87]. However, despite the slowly growing number of health economic evaluations, evidence remains insufficient to draw conclusions. Across all reviews, several common suggestions for future studies were offered: (1) the need for more health economic evaluations across all disorders, (2) including various (active) control conditions and unguided IMIs, (3) focusing on longer time horizons to capture chronicity and productivity losses of disorders, and (4) adhering to economic guidelines using sensitivity and uncertainty analysis, a broad societal

perspective, and (5) using QALYs as clinical effect measures to ensure comparability across studies and willingness to pay (WTP) thresholds to facilitate decision-making.

Given these recommendations and that previous reviews were obsolete and outdated, we designed a systematic review to evaluate the emerging health economic evidence of IMIs in the prevention and treatment of mental problems. Additionally, we intended to include only full health economic evaluations and the assessment of their methodological quality to minimize the heterogeneity and increase the informative value of our findings compared with previous reviews[84,85]. The review was initially planned to evaluate studies published through May of 2018, but was then extended through May of 2021. In line with the existing systematic evidence for the cost-effectiveness of IMIs, we found only a small number of studies targeting SAD and none targeting elevated stress (in employees). One guided iCBT targeting patients with SAD was compared with group CBT from the societal perspective. The iCBT outperformed (dominated) group CBT at 6-month FU, exhibiting a high probability of cost-effectiveness (81% at WTP = 0) for both treatment responder and QALYs gained[88]. After 4 years, the iCBT generated less costs and less effects (treatment responder) but more QALYs gained, ultimately showing a low probability of cost-effectiveness (34% at WTP = £30,000 per QALY gained)[89]. Another study compared an email-guided iCBT and a group CBT to WLC. However, this study failed to report their results, causing relevant costs to remain unclear[90]. Therefore, at the time, our study was the first to evaluate the cost-effectiveness of an unguided IMI targeting SAD.

In conclusion, internet- and mobile-based interventions have a great potential to address known treatment barriers, offer effective treatment, and increase treatment coverage of those affected by mental disorders. At the time our studies were conducted, many important aspects of IMIs remained unclear: sustainable implementation, long-time effects, effects of the level of human guidance, comparison with usual mental healthcare, and costs associated with internet-based treatments. My research should help bridge this evidence gap and inform decision-makers on how to best allocate scarce resources in the healthcare system to maximize treatment outcomes. This leads to the following research questions:

- *What is the short- and long-term efficacy of an unguided internet- and mobile-based self-help intervention for SAD in students?*
- *Does such an intervention represent a good value for money?*
- *Does an iSMI targeting elevated stress in employees represent a good value for money?*
- *What is the cost-effectiveness of psychological IMIs in treatment and prevention of mental problems?*

2. Methodology

2.1 Study 1: Efficacy and Cost-effectiveness of an IMI on SAD

The presented study is part of the World Mental Health International College Student (WMH-ICS) initiative[91] that was executed as the StudiCare project in Germany[92]. The aim was to collect data on mental health based on longitudinal surveys and to develop and evaluate IMIs for college students in terms of their efficacy, acceptance, and cost-effectiveness. Students were recruited inside a network of 19 universities and included if they were aged ≥ 18, German-speaking, exceeded a cut-off score on the reliable and valid Social Phobia Scale[93,94] (SPS > 21) and the Social Interaction Anxiety Scale[93,94] (SIAS > 32). Students were excluded if they showed a risk of suicide, a history of psychotic and bipolar disorders, unstable medication for anxiety and depression, received current psychotherapy, or provided no informed consent. In a two-armed randomized controlled trial (RCT), 200 students with a primary diagnosis of social anxiety disorder (SAD) were randomly assigned to a waitlist control (WLC) or an intervention group (IG). All participants had full access to treatment as usual (TAU). This IMI was offered without human guidance (self-help intervention) but provided standardized automatic reminders and motivational messages for completion to increase adherence (cf. Study Protocol[95]).

The intervention consisted of nine text-based modules based on the cognitive-behavioral treatment by Clark and Wells (1995)[96]. This model proposes that people with SAD hold firm beliefs about the relevance of making a good impression to others while believing that they are making a bad impression on others. Such negative assumptions about themselves and their social environment are due to high self-expectations and negative conditional beliefs. A sense of threat promotes a chain of cognitive, affective, and behavioral responses. Additionally, inter-linked processes take place such as self-focused attention, safety behaviors, processing of oneself as a social object, and worry and rumination before and after a social event. This IMI had been shown to be efficacious in previous studies[97–99]. The modules address various topics: motivational enhancement, reasons to initiate goals and introspection into difficult social situations, psychoeducation, information about maintaining factors (e.g., negative thoughts, safety behavior, self-focused attention) to create an individual SAD model, cognitive restructuring to help identify and modify negative thoughts (thought diary), information on fear of positive evaluation (FPE) to enable the recognition of the devaluation of one's own achievements, self-focused attention, behavioral experiments (in-vivo exposures), and summary and revision. In addition, one module each for healthy lifestyle, problem-solving, and relapse prevention was

offered. Participants were asked to complete one 60-minute module per week consisting of reading the informational material, filling out diaries, and performing exercises.

Assessments were completed at baseline (T0), 10 weeks (T1) and 6-month FU (T2) using a secure web-based assessment system (UNIPARK[100]). Primary outcome measures were SAD symptoms measured via SPS and SIAS. Secondary measures included diagnostic status assessed with the Structured Clinical Interview for DSM-4 Axis I Disorders (SCID-I[101]), interpersonal problems (Inventory of Interpersonal Problems, IPP-64[102]), depression (Beck Depression Inventory II, BDI-II[103]), FPE (Fear of Positive Evaluation Scale, FPES[104]), somatic symptoms (Brief Symptom Inventory, BSI[105]), treatment expectancy (Credibility Expectancy Questionnaire, CEQ[106]) and client satisfaction (German Client Satisfaction Questionnaire, CSQ-8[107]).

Outcomes for the health economic evaluations were treatment response based on the SPS and the SIAS, and QALYs derived from the AQoL-8D (Assessment of Quality of Life[108]). Costs and healthcare utilization were assessed at T0 and T2 with the The Trimbos and iMTA questionnaire for costs associated with psychiatric illness (TiC-P[109]). Healthcare utilization, productivity losses, and patient and family costs were assessed retrospectively (last three months). All costs were calculated in Euro (€) for the reference year 2017. The intervention costs were estimated at €178.50, including maintenance, hosting, and 19% value-added tax (VAT). The area under curve (AUC) method was used to estimate the cumulated costs, linearly interpolating the three months costs at each measurement point to cover the 6-month FU period[110]. Costs were converted to US dollars (US$) using purchasing power parities[111] (reference year 2017).

This study was powered to detect a mean standardized difference of d = 0.40 in the primary outcomes between the groups at post-treatment[95]. All outcomes were analyzed based on intention-to-treat (ITT) principle. Missing data was handled using a Markov chain Monte Carlo multivariate imputation algorithm (N = 10). SPSS[112] was used for the statistical analysis of the efficacy data. Continuous between-group outcomes were analyzed using an analysis of covariance (ANCOVA) with baseline-scores as covariates, post-scores or FU scores as dependent variables as well as identified confounders e.g., previous psychotherapy. The primary outcome analysis (SAD symptoms via SPS, SIAS) was adjusted for multiple testing, α was set at <0.025, and <0.05 for all other tests (outcomes). The effect size was measured via Cohen's d with 95% CI at T1 and T2. Treatment response and deterioration was based on the Reliable Change Index introduced by Jacobson and Truax (1991)[94]. Participants reliably changed when they improved or deteriorated by a certain SAD score (SPS: 7.03, SIAS: 9.53). Participants achieved a symptom-free status if they scored below 18 (SPS) or 27 (SIAS)[94]. Differences in symptom-free status, treatment response and diagnostic status were assessed using the χ^2 test at 6-month FU.

Stata version[113] no 16.1 was used for the health economic evaluation. Missing data was handled using a regression imputation procedure including predictors of the outcome and the dropout. Cost categories were assessed via ordinary least-squares regression (OLS) models from a healthcare and societal perspective. QALYs were estimated using OLS regression models controlling for baseline utility values. Cost-effectiveness (CEA) and cost-utility analyses (CUA) were performed using an incremental cost-effectiveness ratio (ICER) defined as between-group costs delta over the period of 6-months and per unit of effect as QALY gains or symptom-free status. A probabilistic decision-making approach was used,[114] to take the stochastic uncertainty of the trial data into account[115]. Thus, the incremental costs and effects were obtained from a bootstrapped seemingly unrelated regression equations (SURE) model adjusted for baseline utilities, age, and prior psychotherapy[116]. The 5000 bootstrap replications of costs and effect pairs were used to obtain a 95% confidence intervals (CI) and were plotted in a cost-effectiveness plane. Additionally, a cost-effectiveness acceptability curve (CEAC) was presented to show the IMI's cost-effectiveness likelihood at varying WTP ceilings[117]. The robustness of the results was examined by sensitivity analyses including, e.g., per-protocol analysis (study completer), application of the EuroQol Quality of Life 5 Dimensions 5 Level (EQ-5D-5L[118]) to generate QALYs, and increased intervention costs (+50%, +100%).

2.2 Study 2: Cost-effectiveness of an iSMI for employees

The intervention study was planned and conducted by Elena Heber and colleagues[119]. It was part of the GET.ON (GesundheitsTrainings.Online)[120] research project of the Leuphana University Lüneburg, aiming to develop and evaluate the effectiveness of online trainings and apps for health promotion and disease prevention.

Participants were recruited from the general working population via mass media supported by an occupational health management program of the German BARMER health insurance company. Employees were included if they were aged ≥ 18, German-speaking, employed, and exceeded a cut-off score on Perceived Stress Scale-10[121,122] (PSS-10 ≥ 22) and were excluded if they showed a risk of suicide, were diagnosed with psychosis / dissociative symptoms, or provided no informed consent. In a two-armed RCT, 264 participants were randomly assigned to a WLC or an IG. Participants using the web-based and mobile stress-management intervention were supported by an e-coach providing written feedback on a completed session and could, if desired, receive text messages such as automatic motivational text messages and exercises on their mobile phone.

The intervention "GET.ON Stress" consists of 4 modules based upon two main components: problem solving and emotion regulation. The first session includes psychoeducation on emotion- and problem-focused coping strategies and identification of stressors and goal setting. The subsequent two sessions focus on problem solving therapy[123], including six-step problem-solving methods (learning) that are applied to typical and personal scenarios (maintenance). Sessions four to six include emotion regulation techniques based on Affect Regulation Training (ART)[124], applying muscle and beathing relaxation, acceptance and tolerance of emotions and self-support. In the last session, participants reflect on their goals, note early stress warning signs, and write a letter to themselves on how their life have changed after four weeks of practicing the learned methods. Participants were asked to complete one 45-60-minutes module per week including reading the informational material, filling out a daily stress diary and performing exercises and quizzes.

Assessments were completed at baseline (T0), 7 weeks (T1), 6 months FU (T2), and (T3) 12 months FU (only the IG). Primary outcome measures were perceived stress assessed via PSS-10. Secondary outcomes included, e.g., depression (Center for Epidemiological Studies Depression Scale, CES-D[125]), anxiety (Hospital Anxiety and Depression Scales, HADS[126]), emotion regulation (Emotion Regulation Skills Questionnaire (ERSQ-ES[127]), and work engagement and worrying (Utrecht Work Engagement Scale, UWES[128]).

Outcomes for the health economic evaluation were symptom-free status response based on PSS-10, and QALYs derived from the Short-Form Six-Dimension (SF-6D[129]). Costs and healthcare utilization were assessed via the TiC-P[109] at T0 and T2. Healthcare utilization, productivity losses and patient and family costs were assessed retrospectively (last three months). All costs were calculated in Euros (€) for the reference year 2013. The amount of lost working days multiplied by the gross daily wages (based on the monthly salary) was used to calculate absenteeism pursuant to the human capital approach[82]. Working days multiplied by an inefficiency score were used to calculate presenteeism at work (Osterhaus method)[130]. The intervention's costs were based on the current market price at €299 including costs for the development, maintenance, hosting, coaching of participants, and 19% VAT. Cumulated cost were estimated using the AUC method to linearly interpolate three months costs at each measurement point to cover the 6-month FU period. Costs were converted to US dollar (US$) using purchasing power parities (reference year 2013). The statistical analysis of the efficacy outcomes is not part of this thesis and is described elsewhere[131].

Stata[132] version 13 was used for the health economic evaluation. Missing data was handled using a regression imputation procedure including outcome predictors and the dropout.

Clinical outcome data was imputed using a Markov Chain Monte Carlo multivariate imputation algorithm (N = 10). Symptom-free status was achieved if participants scored below 17.70 on the PSS, reflecting more than two standard deviations below the mean of a stressed population (25.52, SD 3.91) at baseline according to Jacobson and Truax (1991)[94].

A CEA and CUA from a societal perspective[133] used an ICER defined by the incremental between-group costs over the period of 6-months and QALY gains or symptom-free status as unit of effect. A probabilistic decision-making approach[114] took the stochastic uncertainty of the trial data into account[115]. Incremental costs and effects were obtained from a bootstrapped SURE model (N = 5000)[116]. The 5000 bootstrap replications of costs and effect pairs were used to obtain 95% CI and were plotted in a cost-effectiveness plane. Additionally, a CEAC was presented to show the IMI's likelihood of being cost-effective at varying WTP ceilings[117].

A cost-benefit analysis (CBA) from an employer's perspective reported (1) net benefits (NB = benefits - costs), (2) the benefit-to-cost ratio (BCR = benefit/cost), (3) and the return-on-investment (ROI = NB/costs). A bias-corrected and accelerated bootstrap procedure (N = 5000) was used to estimate 95% CI[134]. Cost savings were indicated if the following criteria are met: NB > 0, BCR > 1, and ROI > 1[135]. The findings' robustness was examined via sensitivity analyses including, e.g., varying intervention costs (± €100), an alternative instrument EuroQol[118] (EQ-5D-3L) to generate QALYs, and exclusion of outliers (e.g., inpatient costs).

2.3 Study 3: A Systematic Review on Cost -Effectiveness in IMIs

This systematic review provides an overview of the cost-effectiveness of IMIs targeting mental disorders or symptoms. The review is registered on the international prospective register of systematic reviews (PROSPERO (CRD4201809380885)[136] and followed common reporting guidelines (Preferred Reporting Items for Systematic Reviews and Meta-Analyses, PRISMA[137]; Consolidated Health Economic Evaluation Reporting Standards, CHEERS[138]). Several electronic databases were searched: MEDLINE, PsycINFO, Cochrane Central Register of Controlled Trials (CENTRAL), PSYNDEX and National Health Service (NHS) Economic Evaluations Database. Standardized subject terms identified relevant articles published prior to October 5th, 2021, on (1) intervention, treatment, prevention, or psychotherapy, (2) mental disorders, (3) internet, online or mobile-based and (4) economic evaluation. Eligibility criteria based on the PICO framework (Population, Intervention, Comparison, Outcome) were defined as:

Population: Participants with a diagnosis of a mental disorder or symptoms as major depressive disorders, dysthymia, bipolar disorder, social phobia, panic disorder, generalized

anxiety disorder, post-traumatic stress disorder, obsessive-compulsive disorder, specific phobia, and separation anxiety, sleep disorders, or transdiagnostic key-symptoms such as suicidal thoughts, psychological distress assessed on a validated self-report questionnaires or diagnostic interviews.

Intervention: Internet-, online-, web- or mobile-based psychological interventions provided in an online setting based on CBT, interpersonal therapy, problem-solving therapy, positive psychology intervention, psychodynamic therapies, behaviour therapy or behavior modification, systemic therapies, third wave cognitive behavioural therapies, humanistic therapies, or integrative therapies.

Comparators: use of comparators such as other psychological intervention, TAU, WLC or AC group.

Outcomes: Reporting of CEA, CUA, CBA and cost-minimisation analysis (CMA) estimates based on a full economic evaluation where both costs and effects (e.g., QALYs, treatment response, relapse avoided, remission) of two or more alternatives are compared. All eligible studies were RCTs full-text accessible in peer-reviewed English or German scientific journals. Reason for exclusion were: not delivered online, blended intervention (in combination with a F2F or video-based sessions delivered by traditional therapists), reporting of no meaningful outcome measure for economic evaluation, or health economic modelling studies.

Titles and abstracts were screened by two independent researchers during study selection and inter-rater agreement was examined. Data was extracted by applying the CHEERS checklist regarding participants' characteristics, study design, intervention, economic outcome measures, type of economic evaluation, economic evaluation estimates, characteristics of derived costs, and costs perspective. Only results based on the ITT principle were reported. Interventions were judged to be cost-effective when the IMI's effect was higher and costs lower than the comparator's (dominant treatment option). QALYs were cost-effective if their costs were below the WTP threshold of £30,000 as suggested by the National Institute for Health and Clinical Excellence (NICE). Disease-specific clinical outcomes (e.g., treatment response) were judged to be cost-effective when the IMI's probability of cost-effectiveness at a WTP of 0 was equal or greater than 80%. All national currencies were converted to Pound Sterling for the price year 2020 to ensure comparability[139]. Country-specific gross domestic product inflators were used to index the currency to 2020 and subsequently converted to Pound Sterling (£) using purchasing power parities[140].

The quality of the health economic evaluations was assessed by the Consensus on Health Economic Criteria (CHEC[141]). A percental summary score of this 20-item checklist was

used to categorize: excellent (100–95%), good (75%–94%), average (50%–74%) and poor (< 50%). Risk of bias (RoB) was assessed by the Cochrane Collaboration's tool[142] for assessing risk of bias that includes selection, performance, detection, attrition, reporting and other bias in research studies. Performance bias was excluded as participants and personnel cannot be blinded due to the nature of IMIs. RoB was converted to the Agency for Healthcare Research and Quality standards[143] (i.e., good, fair, or poor quality). Both RoB and CHEC were rated independently by Fanny Kählke and Claudia Buntrock.

3. Publications and Submissions

1. **Kählke, F.,** Berger, T., Schulz, A., Baumeister, H., Berking, M., Cuijpers, P., Bruffaerts, R., Auerbach, R.P., Kessler, R.C., Ebert D.D. Efficacy and cost-effectiveness of an unguided, internet- and mobile-based self-help intervention for social anxiety disorder in university students: protocol of a randomized controlled trial. *BMC Psychiatry* **19**, 197 (2019). https://doi.org/10.1186/s12888-019-2125-4

2. **Kählke, F.**, Berger, T., Schulz, A., Baumeister, H., Berking, M., Auerbach, R.P., Bruffaerts, R., Cuijpers, P., Kessler, R.C., Ebert D.D. Efficacy of an Unguided Internet-Based Self-Help Intervention for Social Anxiety Disorder in University Students: A Randomized Controlled Trial. *International Journal of Methods in Psychiatric Research* **28**, e1766 (2019). https://doi.org/10.1002/mpr.1766

3. **Kählke, F.**, Buntrock, C., Smit, F., Berger, T., Baumeister, H., Ebert, D.D. Long-term Outcomes and Cost-effectiveness of an Internet- and Mobile-based Self-help Intervention for Social Anxiety Disorder in University Students: A Randomized Controlled Trial. *Nature Human Behavior,* **Under Review** (2022).

4. Ebert, D.D., **Kählke F.**, Buntrock, C., Berking, M., Smit, F., Heber, E., Baumeister, H., Funk, B., Riper, H., Lehr, D. A Health Economic Outcome Evaluation of an Internet-Based Mobile-Supported Stress Management Intervention for Employees. *Scandinavian Journal of Work, Environment & Health* **44**, 171-182 (2018). https://doi.org/10.5271/sjweh.3691

5. **Kählke, F.**, Buntrock, C., Smit, F., Berking, M., Lehr, D., Heber, E., Funk, B., Riper, H., Ebert, D.D. Economic Evaluation of an Internet-Based Stress-Management Intervention Alongside a Randomized Controlled Trial *Journal of Medical Internet Research Mental Health* **6**, e10866 (2019). https://doi.org/10.2196/10866

6. **Kählke, F.,** Buntrock, C., Smit, F., Ebert, D.D. Systematic review of economic evaluations for Internet- and mobile-based interventions for mental health problems *Nature Digital Medicine* (2022). https//doi.org/10.1038/s41746-022-00702-w

3.1 Article 1: Study protocol – IMI for Students with SAD

Authors: Fanny Kählke, Thomas Berger, Ava Schulz, Harald Baumeister, Matthias Berking, Pim Cuijpers, Ronny Bruffaerts, Randy P. Auerbach, Ronald C. Kessler & David D. Ebert
Title: Efficacy and cost-effectiveness of an unguided, internet- and mobile-based self-help intervention for social anxiety disorder in university students: protocol of a randomized controlled trial.
Journal: *BMC Psychiatry*, Vol. 19, No. 197 (2019) https://bmcpsychiatry.biomedcentral.com/articles/10.1186/s12888-019-2125-4
DOI: https://doi.org/10.1186/s12888-019-2125-4
Trial register: https://www.drks.de/DRKS00011424

Social anxiety disorder (SAD) is prevalent among college students. Adverse consequences of SAD are problems with identity formation, low quality of life, suicidal ideation, and high alcohol consumption. They lead to an economic burden stretching beyond treatment costs such as decreased productivity and lower qualification. Students with SAD often fear to be stigmatized or evaluated negatively and hence remain untreated. Unguided internet- and mobile-based self-help interventions (IMIs) can address treatment barriers. This study examines the efficacy and cost-effectiveness of an IMI targeting SAD in students. In this two-armed randomized controlled trial, 200 students aged 18 years or above showing a primary diagnosis of SAD (Social Phobia Scale [SPS ≥ 21] or Social Interaction Anxiety [SIAS ≥ 32]) were assigned at random to an intervention group (IG) (n = 100) or a waitlist control (WLC) (n = 100) group with unrestricted access to treatment as usual (TAU). All students had full access to TAU. The intervention was adapted to student needs and additionally offers one module based on fear of positive evaluations, a neglected determinant of the SAD treatment. The IMI includes 9 modules based on the cognitive-behavioral approach by Clark and Wells (1995) including: psychoeducation, avoidance and safety behavior, self-focused attention, cognitive restructuring of dysfunctional assumptions, fear of positive evaluation, and behavioral experiments. The content includes text, protocols, diaries, and exercises. The self-help intervention is not supported by a therapist but applies automated standardized reminders and motivational text messages to increase adherence. The study outcomes were assessed at baseline, 10 weeks and 6-month follow-up. The primary outcome were SAD symptoms at post-treatment. Secondary outcomes included, among others, diagnostic status, costs, quality of life, depressive symptomatology, and fear of positive evaluation. Diagnostic status was assessed through a Structured Clinical

Interview for DSM-4 Axis I Disorders (SCID-I). Health economic evaluations included cost-effectiveness and cost-utility analyses from a societal and health provider perspective.

The manuscript was submitted in May 2018, accepted in April 2019, and published under the terms of Creative Commons Attribution 4.0 license (manuscript can be reproduced) in June 2019 in the section Study Protocol of the Journal *BMC Psychiatry*. *BMC Psychiatry* is an international open access, peer-reviewed journal publishing articles on all aspects of the prevention, diagnosis, and management of psychiatric disorders.

Contribution: Fanny Kählke was the principal investigator of the study and author of the published article. David D. Ebert and Harald Baumeister obtained funding for this study as part of the StudiCare project. Thomas Berger developed the evaluated intervention. Fanny Kählke supported by David D. Ebert, Thomas Berger, Ava Schulz developed the conception of the study design. She wrote the published article and was supervised by David D. Ebert. All co-authors read, critically revised, and finally approved the published article.

BMC Psychiatry

STUDY PROTOCOL Open Access

Efficacy and cost-effectiveness of an unguided, internet-based self-help intervention for social anxiety disorder in university students: protocol of a randomized controlled trial

Fanny Kählke[1*], Thomas Berger[2], Ava Schulz[9], Harald Baumeister[3], Matthias Berking[1], Pim Cuijpers[4], Ronny Bruffaerts[5], Randy P. Auerbach[6,7], Ronald C. Kessler[8] and David Daniel Ebert[4]

Abstract

Background: Social anxiety disorder (SAD) is highly prevalent among university students, but the majority of affected students remain untreated. Internet- and mobile-based self-help interventions (IMIs) may be a promising strategy to address this unmet need. This study aims to investigate the efficacy and cost-effectiveness of an unguided internet-based treatment for SAD among university students. The intervention is optimized for the treatment of university students and includes one module targeting fear of positive evaluations that is a neglected aspect of SAD treatment.

Methods: The study is a two arm randomized controlled trial in which 200 university students with a primary diagnosis of SAD will be assigned randomly to either a wait-list control group (WLC) or the intervention group (IG). The intervention consists of 9 sessions of an internet-based cognitive-behavioral treatment, which also includes a module on fear of positive evaluation (FPE). Guidance is delivered only on the basis of standardized automatic messages, consisting of positive reinforcements for session completion, reminders, and motivational messages in response to non-adherence. All participants will additionally have full access to treatment as usual. Diagnostic status will be assessed through Structured Clinical Interviews for DSM Disorders (SCID). Assessments will be completed at baseline, 10 weeks and 6-month follow-up. The primary outcome will be SAD symptoms at post-treatment, assessed via the Social Phobia Scale (SPS) and the Social Interaction Anxiety Scale (SIAS). Secondary outcomes will include diagnostic status, depression, quality of life and fear of positive evaluation. Cost-effectiveness and cost-utility analyses will be evaluated from a societal and health provider perspective.

Discussion: Results of this study will contribute to growing evidence for the efficacy and cost-effectiveness of unguided IMIs for the treatment of SAD in university students. Consequently, this trial may provide valuable information for policy makers and clinicians regarding the allocation of limited treatment resources to such interventions.

Trial registration: DRKS00011424 (German Clinical Trials Register (DRKS)) Registered 14/12/2016.

Keywords: Social anxiety disorder, Social phobia, Randomized controlled trial, Internet-based treatment, Self-help, Unguided self-help, University students, Economic evaluation

* Correspondence: fanny.kaehlke@fau.de
[1]Friedrich-Alexander-University Erlangen-Nürnberg (FAU), Nägelsbachstrasse 25a, 91052 Erlangen, Germany
Full list of author information is available at the end of the article

Background

Anxiety disorders have the highest prevalence compared to other mental health disorders, showing an estimated lifetime prevalence of 10–22% in European Countries [1]. Social anxiety disorder (SAD) is ranked as the third most common anxiety disorder in Germany [2], and the prevalence estimates of SAD in university students range from 3.4% (12-month) in the United States [3] to 16.1% (point-prevalence) in Sweden [4].

SAD among university students has been associated with a number of adverse effects, including low quality of life [5] and problems with identity formation [6], increased consumption of alcohol [7] and high levels of suicidal ideation [8]. Additionally, SAD-related emotional distress causes dysfunctional avoidance strategies, which are associated with underachievement and may lead to premature drop out from university [4]. Therefore, the economic burden extends beyond the direct costs of treatment to indirect costs (e.g. low productivity, increased number of sick days, lower qualification level [9, 10]) and intangible costs (e.g. reduced quality of life, social impairment). Thus, treatment of SAD is of particular interest to the public healthcare system and health services in and outside of university [11, 12], especially as SAD may become a chronic condition when left untreated [13].

Effective treatment options exist [14, 15], but are only used by a small proportion of those in need [16, 17]. Reasons for low treatment rates include not only a limited availability of trained clinicians but also other barriers to help-seeking such as fear of stigmatization. Fear of negative evaluation, the expectation that others might judge one's behavior or physical symptoms as embarrassing or humiliating, [18, 19] is the key feature of SAD. Hence, the nature of SAD is one major reason which prevents university students from seeking professional advice [9, 20].

Internet- and mobile-based interventions are a promising strategy to reach underserved SAD populations. In contrast to traditional face-to-face therapy IMIs are immediately accessible, lack stigmatization, are more flexible, anonymous, and initiated with minimal (or no) human contact [21–23]. In addition, although the initial costs of developing an IMI can be quite high, the low marginal costs of providing IMIs to additional user are assumed to lead to lower overall expenditures [24]. Moreover, IMIs are likely to reduce health care delivery costs compared to face-to-face treatment, as IMIs involve minimal or no contact with mental health care specialists and also reduce travel costs.

A large number of studies have shown that IMIs can be effective in the treatment of common mental disorders [22]. The most recent systematic review on IMIs for SAD showed a mean standardized effect size of g = 0.84 [0.72–0.97] compared to untreated control groups and g = 0.38 [0.13–0.62] compared to active control conditions [25]. We are aware of only one small study (n = 38) that evaluated a psychological internet supported intervention for SAD in university students [26]. This study assessed an internet-based self-help intervention with minimal email contact to a psychotherapist with in vivo group exposure compared to no in vivo group exposure. The intervention resulted in large pre-post within-group effect-sizes for both groups. The generalizability of these results are, however, limited due to methodological shortcomings (e.g. small sample size). In addition, the study did evaluate neither the cost-effectiveness of the intervention nor the effects of unguided self-help.

One of the major cost-drivers and potential barriers for large-scale treatment dissemination is the provided level of therapeutic guidance in IMIs. In a recent meta-analysis guided IMIs yielded a mean average effect of g = 0.87 [0.72–1.02] compared to passive control conditions such as WLC (n = 11) [25]. The standardized effect size of unguided IMIs was g = 0.78 [0.50–1.05] compared to passive controls (n = 8). The effect sizes (0.28–1.47) varied widely between unguided IMIs [27–34], which makes it difficult to anticipate the expected effect size for future studies. We suspect that the variance in effect sizes between studies could be explained by methodological differences such as small (n = 20–40) [27, 29–32] to moderate (n = 56–62) [28, 34] sample sizes, different lengths of follow-ups (e.g. only three studies evaluated long-term effects [27–29]) and high dropout rates. Therefore, additional research is needed to determine the efficacy of unguided internet-based interventions in the treatment of SAD, particularly among university students.

Although it is often assumed that IMIs tend to be cost-effective, there is limited empirical evidence showing the impact on health economic outcomes [35–37]. To the best of our knowledge, only three studies investigated the cost-effectiveness of IMIs for SAD; all of these studies evaluated a therapist guided IMI [38–40]. To date, no study has investigated the cost-effectiveness of an internet-based intervention in university students, and no study has evaluated the health economic effects of an unguided internet-based intervention for SAD.

Although the efficacy of Cognitive Behavioral Therapy (CBT) in the treatment of SAD is well-documented, there is still room for improvement. Recent findings suggest not only fear of negative evaluations to be a central feature of SAD, but also prove a strong link between SAD and the fear of positive evaluation (FPE) [41–43]. According to Weeks and Howell's (2012) bivalent fear of evaluation model of social phobia, fear of evaluation in general is the core component of SAD, including the

fear of negative (FNE) and positive evaluation [44]. The function of FPE in SAD also has been discussed in the context of evolutionary models of social anxiety [45]. Empirical evidence shows that FPE and FNE are related but distinct factors contributing to SAD, with FPE explaining a unique and independent proportion of variance in the fear of social interactions [46]. Even though established treatments for SAD do not address FPE directly, there is evidence that CBT can reduce FPE, albeit with smaller effect sizes compared to FNE [42]. And, importantly, neglecting FPE in SAD treatments may impede treatment progress (e.g., when clients still feel anxious after successful exposures that received positive feedback) [47]. Specifically, people who endorse FPE do not feel proud when making progress or achieving goals and, paradoxically, often experience discomfort [41]. In that sense, FPE often results in socially anxious people avoiding social situations in which they are the focal point (e.g., group work, presentations at university) which prevents their exposure to positive social feedback and safeguards their social status within the group [42, 48]. Although research has shown that FPE is responsive to cognitive-behavioral therapy [49], no intervention has systematically addressed this as a treatment component of SAD.

The aim of this study will be to evaluate whether an unguided internet-based intervention for SAD is effective in reducing social anxiety symptoms and other secondary outcomes such as depression, fear of positive evaluation, interpersonal problems and quality of life when compared to a WLC in university students. Additionally, cost-effectiveness analyses will be conducted from societal and health provider perspective in order to examine whether this internet-based intervention for SAD represents good value for money.

This study is part of the recently launched Caring Universities – the World Health Organization (WHO) World Mental Health International College Student (WMH-ICS) initiative (https://www.hcp.med.harvard.edu/wmh/college_student_survey.php) [50, 51]. It is an international initiative which aims to obtain accurate cross-national data on the prevalence, and correlates of mental disorders among university students throughout the world, assess unmet needs for treatment, develop practical methods to improve mental health intervention utilization, and evaluate effective strategies for the prevention and treatment of mental health disorders in university students.

Methods

Study design

This study is a randomized-controlled trial in which the assumed superiority of an internet-based intervention for SAD is evaluated compared to a WLC. The intervention group will receive the internet-based self-help treatment for social anxiety and the control group will obtain access to this intervention after 6 months. Both conditions have full access to university and community treatment as usual.

Participants

We anticipate recruiting a total of $N = 200$ participants of which 100 participants will be assigned to each of the two conditions. Participants will be recruited in Germany, Austria and Switzerland. The recruitment strategy consists of various components: a study website, a promotional video, postings to Facebook and Internet forums and an email with information of the study sent to all German, Swiss and Austrian university psychological counseling centers and all students attending different universities based in Ulm, FAU, Bern, Dresden, Hagen, and Vienna. The study flow is illustrated in Fig. 1.

Inclusion criteria

Participants will be included if they

- are a student,
- are at least 18 years old,
- have internet access,
- have sufficient German language skills as assessed via self-report ("Do you speak and understand German?"),
- exceed predefined cut-off scores in the SPS or SIAS,
- fulfill the diagnostic criteria of SAD according to DSM-IV assessed via a SCID-I diagnostic interview,
- have the ability to provide a written informed consent.

Exclusion criteria

Participants will be excluded if they,

- show an acute suicidal risk according to the suicide item of the Beck Depression Inventory II (BDI II) (score > 1) or the diagnostic interview,
- have a history of psychotic or bipolar disorders,
- and are receiving psychotherapy at the time of entering the study.
- Prescription medications for anxiety and depression lead to an exclusion if the dosage was changed one month before the beginning of the study.

Randomization

Two hundred participants will be randomly assigned. The allocation list is produced by a random number generator Randlist [9] which randomly allocates participants in a 1:1 ratio with a block size of 8 to either IMI or WLC. The list is operated by an independent

researcher not otherwise involved in the study. This researcher has no information about the participants other than the participants's trial ID numbers and will randomize the participants in the order of the incoming informed consent form. During the randomization process, the allocation will be concealed from participants and researchers involved in recruitment. Participants will not be blinded to study conditions.

Internet-based self-help intervention with an additional session on fear of positive evaluation

The intervention is based on the well-established cognitive-behavioral treatment of Clark and Wells (1995) [52] and has been shown to be efficacious in several previous studies [27, 53–56]. It consists of nine text-based sessions, various exercises (e.g. attention training) and diaries (such as a diary to identify and question negative thoughts). Participants are advised to complete one session per week, review the exercises, and complete diaries. The approximate time required to complete one session is 60 min, and participants are encouraged to practice the strategies in their daily life. An overview of the sessions is summarized in Table 1. The original intervention was tailored to the university setting, for example, by providing case examples of socially anxious students.

An additional module in session 4 not part of the original Clark and Wells program targets FPE. FPE is defined as discomfort and fear in reaction to positive feedback from others. The module contains psychoeducational material regarding the definition and etiology of FPE according to the bivalent fear of evaluation model [44] and the evolutionary model [45], as well as information on FPE-related cognitive strategies such as the disqualification of positive social outcomes (DPSO). A thought diary is introduced to identify and modify FPE-related cognitions, including perceived costs and advantages of positive evaluation. Additionally, the module contains exercises that aim at promoting self-compassion as well as the experience and acceptance of positive emotions which have been linked to a decrease of FPE [57].

Although this is a therapeutically unguided self-help intervention, guidance is provided via standardized automatic messages aiming to promote adherence. Adherence reminders follow procedures used in a number of previously conducted studies [58–60]. They consist of one positive reinforcement per session completion and one automatic reminder if participants do not log into the platform for more than one week. These automated reminders contain standardized personalized motivational messages, which strengthen participants' adherence to the intervention.

Table 1 Session content for the SAD internet-based self-help program

Session	Intervention content
Session 1 Motivational enhancement	Reasons to initiate change, defining goals and recoding introspection of difficult social situations with help of an anxiety protocol
Session 2 Psychoeducation	Information on SAD and maintaining factors such as negative thoughts, safety behaviors and self-focused attention
	Development of an individual model for SAD
Session 3 Cognitive restructuring	Identification and modification of negative thoughts (dysfunctional assumptions) with the help of a thought diary
Session 4 Fear of positive (social) evaluation	Information about FPE (examples and explanatory models)
	Identifying FPE using a diary
	Recognizing the devaluation of own achievements, the benefit and the risks of positive evaluation using a diary
	Endorsing positive evaluations and emotions applying a self-compassion-interventions
Session 5 Self-focused attention	Various exercises to reduce self-focused attention
Session 6 Behavioral experiments	Planning and conducting in-vivo exposures
Session 7 Summary and revision	Summary of the key elements of the training
	Highlighting the importance of revising the exercises (e.g. in-vivo exposure)
Session 8 Healthy lifestyle and problem solving	Information about healthy lifestyle (e.g. sports, nutrition)
	Conveying problem solving skills
Session 9 Relapse prevention	Strategies to maintain the acquired skills
	Preparing for possible relapses

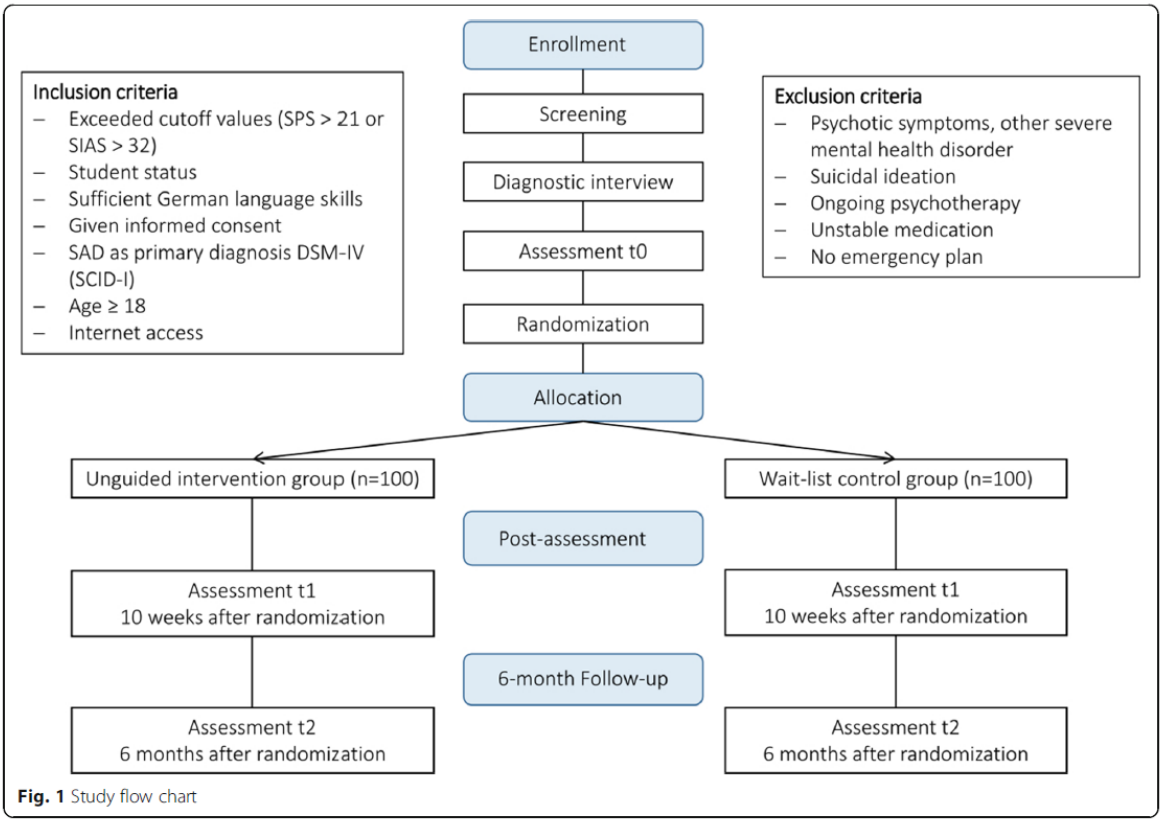


Fig. 1 Study flow chart

Procedure

Students who are interested in enrolling in the study will contact the study team through a contact form from a student mental health platform (i.e., on www.studicare.com) or directly via email. If participants satisfy inclusion criteria they will be randomly assigned to either the IG or the WLC. Students who are assigned to the IG can initiate the online-based self-help intervention immediately after randomization. Students in the WLC will receive access to the program six months after randomization. The study includes three assessments: both groups are assessed at baseline (t0), immediately after completing the program (t1; 10 weeks) and at follow-up six months after randomization (t2). The assessment at t1 (10 weeks) is independent from treatment completion. Treatment adherence will be monitored after t1. Self-reported measures are collected using a secure web-based assessment system (UNIPARK, 256-bit encrypted [61]). This system allows for data validation (range checks, double data entries) to improve data quality. Additionally, participants' SAD symptoms in IG will be assessed weekly via the intervention platform. The collected data will be stored securely.

Measurements

A detailed overview of all measures at baseline (t0), 10-week post-treatment (t1) and 6-month follow-up is given in Table 2.

Primary outcome measures

Symptoms of SAD

The primary outcome is SAD symptoms. SAD symptoms will be measured with two widely used measures, the Social Phobia Scale and the Social Interaction Anxiety Scale (SPS & SIAS; [62]). These two self-report questionnaires complement one another and are usually administered together. The SIAS assesses more general fears of social interaction (e.g., "I tense up if I meet an acquaintance in the street"), while the SPS focuses on fears of being judged by others during daily activities (e.g., "I become anxious if I have to write in front of others."). Both scales consist of 20 items to be rated on a 5-point Likert scale (0= "not at all" to 4 = "extremely"). These two companion measures have been found to be valid, reliable and useful for clinical and research purposes [63]. Cronbach alphas for the SIAS and SPS range from 0.90 to 0.94 [64].

Table 2 Measurements and time of assessment

Instrument	Abbreviation	Aim	Time of assessment		
			t0	t1	t2
Clinician administered					
Structured Clinical Interview for DSM-IV Axis I Disorders	SCID-I	DSM-IV Axis I disorders	✓		✓
Self-report ratings					
Primary Outcome Measure					
Social Phobia Scale[a]	SPS	Symptoms of SAD	✓	✓	✓
Social Interaction Anxiety Scale[a]	SIAS	Symptoms of SAD	✓	✓	✓
Secondary Outcome Measure					
Liebowitz Social Anxiety Scale	LSAS-SR	Social anxiety symptoms	✓	✓	✓
Beck Depression Inventory II	BDI-II	Symptoms of depression	✓	✓	✓
Brief Symptom Inventory	BSI	Psychiatric symptoms	✓	✓	✓
Inventory of Interpersonal Problems	IIP-64	Interpersonal problems	✓	✓	✓
Fear of Positive Evaluation Scale	FPES	Fear of positive evaluation	✓	✓	✓
Disqualification of Positive Social Outcomes Scale	DPSOS	Fear of positive evaluation	✓	✓	✓
EuroQol (EQ-5D-5 L)	EQ-5D-5 L	Quality of life	✓	✓	✓
Assessment of Quality of Life (AQol)	AQoL-8D	Quality of life	✓	✓	✓
Client Satisfaction Questionnaire	CSQ-8	Client satisfaction		✓	
Trimbos/iMTA Questionnaire for Costs associated with Psychiatric Illness	TiC-P	Cost-effectiveness	✓		✓
Credibility Expectancy Questionnaire	CEQ	Treatment expectancy	✓		

t0 Baseline; t1 10 weeks; t2 6 months; Assessments ✓ = intervention and control group; ✓ = intervention group [a] process measures assessed every 2 weeks

Secondary outcome and process measures

Diagnostic status

The diagnostic status will be assessed with the Structured Clinical Interview for DSM-IV (SCID-I [65]). The interview will be conducted and recorded by trained raters (clinical psychologists or graduate students in psychology) via telephone at baseline and 6-months. The raters are blind to the condition the participants are assigned to. In order to ensure blinding, (a) participants receive information on the importance of not informing interviewers about the conditions they were assigned to, (b) raters receive a written reminder to not ask the participants for their randomization status, (c) written and verbal reminders for the participants before the interview; and (d) a documentation after the interview if the rater is still blind to treatment condition. The inter-rater reliability will be evaluated through a random selection of 10% of recorded cases.

Beck depression inventory II

Depression severity will be assessed using the Beck Depression Inventory II (BDI-II) [66]. The scale consists of 21 items each rated on a 4-point Likert-scale. Prior research has shown high reliability and validity in SAD clients [27].

Brief symptom inventory

General psychopathology will be assessed using the Brief Symptom inventory (BSI), which spans 9 dimensions, including insecurity in social situations, anxiety, depressiveness and compulsivity [67]. The BSI assesses symptoms within the past week and has shown robust psychometric properties [68]. The Global Severity Index (GSI), the overall mean score, will be reported.

Liebowitz social anxiety scale

The Liebowitz Social Anxiety Scale (LSAS) [69, 70] is a self-report scale that assesses fear and avoidance in 24 different situations. Thirteen of the situations relate to performance and the remaining items assess situations within the context of social interactions. Prior research has shown good to excellent reliability and validity (Cronbach's alphas ranging from 0.83 to 0.94) [69].

Inventory of interpersonal problems

Difficulties in interpersonal behavior and sources of relational distress will be assessed using the Inventory of Interpersonal Problems (IIP-64) since they indicate assertiveness and passivity of participants. The instrument has eight dimensions and has shown adequate psychometric properties (Cronbach's alphas ranging from 0.71 to 0.82) [71, 72].

Fear of positive evaluation

Fear of positive social feedback will be assessed using the Fear of Positive Evaluation Scale [73]. The FPES is a

self-report measure consisting of 10 items and has shown good psychometric properties in clinical and healthy samples [49, 73].

The disqualification of positive social outcomes (DPSO) is a cognitive strategy which has been linked to FPE [44, 73]. This cognitive tendency is proposed to serve as a mental safety behavior in the context of FPE and will be measured using the Disqualification of Positive Social Outcomes Scale (DPSOS) [74]). The DPSOS is designed to measure the disqualification of positive outcomes on two dimensions, other-oriented attributions (e.g., "people will laugh at my jokes even if they are not funny") and self-oriented attributions that refer directly to DPSO (e.g., "I frequently dismiss my own social successes and accomplishments").

Quality of life

The Assessment of Quality of Life (AQol) [75] and the EuropeanQuality of Life 5 Dimensions 3 Level (EQ-5D-5L) instrument [76, 77] will assess quality of life. The AQol assesses eight dimensions (independent living, pain, senses, mental health, happiness, coping, relationships, self-worth) and allows for the calculation of separate sum scores for each dimension. The EQ-5D is a widely applied, valid and reliable measurement of quality of life. It consists of five items on a five-point Likert scale related to mobility, self-care, common activities, pain/discomfort and anxiety/depression. Additionally, this measure contains a visual analogue scale (VAS) to assess the respondent's self-rated health status. Only the AQoL will be used as a secondary outcome, the EQ-5D will only be used for sensitivity analyses in the health economic outcome evaluation.

Cost measures

The Trimbos and iMTA Treatment Inventory of Costs in Patients with psychiatric disorders (TIC-P) [78] was adapted for the application to the German health care system and the specific target group. Direct medical costs (e.g., drugs), direct non-medical costs (e.g., transportation) and indirect costs (e.g., productivity losses) [79] will be assessed over a period of the previous 3 months. A catalog of German unit costs [80] will be used to calculate total health care costs on individual basis assuming that the majority of participants will be from Germany [81]. Indirect non-medical cost stemming from productivity losses due to presenteeism and absenteeism costs will be assessed with specific modules of the TiC-P. From a student's perspective a monthly rate that students are paid due to the German Federal Law on Support in Education (BAföG) [82] is assumed covering the general cost for living and education in Germany. The intervention costs are estimated at €150 ($181) per participant. This tariff stems from a health care provider (GET.ON Institute) that offers comparable internet-based interventions. Including German VAT of 19%, interventions costs were €178.50.

Other measures

Other assessments will include demographic variables (e.g., age, gender, student status, etc.). Moreover, a version of the German Client Satisfaction Questionnaire (CSQ-8) [83] that was adapted to the online training context will assess the acceptance of internet-based interventions and global client satisfaction on the intervention [84]. Adherence to treatment will be evaluated by completion rate and time spent in intervention. The 6-item German version of the Credibility Expectancy Questionnaire (CEQ) [85] assesses the intervention's credibility and outcome expectancies. Additionally, credit points based on the European Credit Transfer System (ECTS) [86] are assessed to evaluate the reduced academic productivity.

Process measures

Participants in the active conditions will be asked to rate their symptoms of SAD every two weeks (SPS & SIAS) in order to detect change in social phobic symptoms during the intervention.

Power and sample size calculation

The study is powered to detect small to medium effect sizes of d = 0.4. The intended sample size of 200 participants will provide sufficient power to detect a significant standardized effect size (Cohen's d) of 0.4 on the primary outcome variable (symptoms of SAD via SPS and SIAS) between the two conditions. The software Gpower [87] was used to calculate the sample size of $n = 100$ per group given a Bonferroni-adjusted (due to multiple testing) alpha error level of 0.025 for a one-sided test, a statistical power of 0.80 and an effects size of d = 0.4.

Analysis

Analyses will be conducted and reported according to the Consolidated Standards of Reporting Trials (CONSORT) statement [88]. The results will be disseminated in peer-reviewed scientific journals. The depersonalized data will be analyzed based on the intention-to-treat principle. Missing data will be handled using multiple imputations with 10 estimations per missing value following recommendations of Little and Rubin [89] and Schafer [90]. Differences in continuous outcomes between the groups will be analyzed using analysis of covariance (ANCOVA), with pre-scores as a covariate and the post-scores as the dependent variable. Possible confounders (e.g. former use of psychotherapy) will be assessed and included as covariates if they should be associated with changes in the primary outcome. We

will compute standardized effect sizes (Cohen's d including the 95% confidence intervals for all effect sizes). We will also test differences in treatment response rates (50% relative symptom reduction), numbers of participants displaying reliable change (according to Jacobson and Truax [91]) as well as differences in symptom deterioration rates. Effect sizes between groups of dichotomous outcome variables will be expressed as number needed to treat and its associated 95% confidence intervals. All reported p-values are (one-sided) at a significance level of 0.025 for the primary outcomes and 0.05 for the secondary outcomes.

Moderators of the outcome will be analyzed on an exploratory basis using regression analyses, as well as region of significance procedures [92], in case of significant findings. Baseline variables considered for moderator analyses include: Sociodemographic and study-related characteristics (e.g. age, gender, nationality, full-time versus part-time students, study major, number of semesters on leave, number of semesters in total, ECTS points), baseline severity of social phobia (SIAS, SPS), depressive (BDI-II) and general psychopathological symptoms (BSI), interpersonal problems (IIP), fear of positive evaluations (FPE), health-related quality of life (AQoL), generalized vs. specific SAD, concurrent use of psychotropic drugs, prior mental health treatment, perceived treatment credibility (CEQ), comorbid depressive disorders (SCID), number of comorbid disorders (SCID), age of onset (SCID). Moderator analyses will not be adjusted for multiple testing, as the aim is to generate hypotheses to be tested in future confirmative studies. All directional hypotheses are tested one-sided, bidirectional hypotheses two sided.

Economic evaluation

We will perform an economic evaluation from the societal and health provider perspectives that include all relevant costs and outcomes. A cost-effectiveness analysis as well as a cost-utility analysis will be conducted following guidelines from the International Society for Pharmacoeconomics and Outcomes Research (ISPOR) Good Research Practices Task Force Report and the recommendations of the Consolidated Health Economic Evaluation Reporting Standard (CHEERS) [93, 94]. In the cost-effectiveness analyses, symptom-free status via SPS and SIAS will be used as clinical outcome. For cost-utility analyses, quality-adjusted life years (QALYs) will be calculated based on the AQOL-8D. EQ-5D-5L will be used only in sensitivity analyses. We will compare both groups in terms of incremental costs and incremental effects, by calculating the incremental cost-effectiveness ratio (ICER). We will use bootstrapping ($N = 5000$) and 95% confidence intervals in percentiles to test the robustness of the ICER and to quantify the uncertainty surrounding the ratios. The results will be shown in a cost-effectiveness plane and in a cost-effective acceptability curve. Additionally, the robustness of the base-case findings will be tested with a multi-way sensitivity analysis (i.e. ± 50% intervention costs, costs outliers, EQ-5D-5L as alternative instrument to calculate QALYs).

Discussion

SAD is a highly prevalent mental health disorder, also among university students. Affected students suffer from lower quality of life, high burden of psychological strain and reduced academic functioning. Internet-based interventions represent a low-threshold, easily accessible, and flexible treatment which may help to overcome the low utilization rates of those in need.

Within this study we intend to extend the evidence of internet-based self-help for SAD regarding efficacy and cost-effectiveness. Particularly, we want to strengthen the evidence of unguided treatments, since the question how much support is needed remains unanswered given prior mixed results. On the one hand, results from two meta-analyses [95, 96] found self-help programs with support to be more effective and with lower attrition rates compared to no support. Whereas a recent meta-analysis on internet-based guided cognitive behavioral interventions for anxiety disorders in general did not find such differences, indicating that effects between current guided and unguided treatments for anxiety might be smaller than previously anticipated [25].

There may be several other factors such as the intensity of screening procedures [53], the length, structure and comprehensiveness of the self-help program itself [97], the extent of support needed depending on the disorder [96] as well as human substitutes such as automated reminders [98], which systematically confound whether guided interventions lead to superior results compared to unguided interventions [99].

This study will have three noteworthy limitations. First, if this study demonstrates clinically relevant effects for unguided self-help for SAD, it has to be taken into account that this evidence will be based on an RCT, which is characterized by a highly structured participation and research attention. This is usually not the case when self-help interventions are offered in routine care. Since the securing of commitment represents an adherence-promoting element in self-help interventions, it has been argued that effect sizes of pure self-guided interventions found in RCTs are significantly overestimated for what can be expected in routine care [100], when no additional measures to increase adherence are applied. Hence, in order to achieve similar effects outside laboratory conditions, a clear concept for ensuring

adherence through minimal guidance from a professional or lay health worker seems favorable.

Second, we will employ an open recruitment strategy in the general student population. Such a procedure mimics a public health approach of student mental health treatment barriers of face-to-face treatment pathways. However, results need to be interpreted cautiously in such a context and may not generalize to classical routine face-to-face clinical practice pathways. A previous study has found that patients undergoing internet-based treatment resembled national general samples more closely than samples from routine face-to-face mental health care [101].

Third, the cost assessment is based on a self-report instrument and it may be argued that self-report data are potentially less accurate compared to data collected directly from public registers. However, comparative studies of self-report questionnaires and diaries have found an acceptable comparability [102]. The remaining risk, however, is likely to be equal across treatments, making it unlikely that it will result in a bias between groups.

Conclusion

To the best of our knowledge, this study will have the largest unguided RCT intervention group recruited for SAD treatment so far [15, 103]. This study will contribute to the evidence for the efficacy, cost-effectiveness and moderators of unguided internet-based self-help for social phobia in university students. If successful, this intervention would facilitate the adequate allocation of scarce resources and will provide valuable information of a public health approach of SAD treatment. When implemented on large scale, such interventions might help to reduce the immense burden associated with SAD in university students.

Abbreviations

ANCOVA: Analysis of covariance; AQol: Assessment of Quality of Life; BAföG: German Federal Law on Support in Education; BDI-II: Beck Depression Inventory II; BSI: Brief Symptom inventory; CBT: Cognitive behavioral therapy; CEQ: Credibility expectancy questionnaire; CHEERS: Consolidated Health Economic Evaluation Reporting Standard; CSQ-8: German Client satisfaction questionnaire; DPSO: Disqualification of positive social outcomes; DRKS: German Clinical Trials Register; ECTS: European Credit Transfer System; EQ-5D-5L: European Quality of Life 5 Dimensions 3 Level instrument; FNE: Fear of negative; FPE: Fear of positive evaluation; ICER: Cost-effectiveness ratio; IG: Intervention group; IIP-64: Inventory of Interpersonal Problems; IMI: Internet- and mobile-based self-help intervention; ISPOR: International Society for Pharmacoeconomics and Outcomes Research; LSAS: Liebowitz Social Anxiety Scale; QALYs: Quality-adjusted life years; RCT: Randomized controlled trial; SAD: Social anxiety disorder; SCID: Structured Clinical Interview for DSM Disorders; SIAS: Social Interaction Anxiety Scale; SPS: Social Phobia Scale; TIC-P: The Trimbos and iMTA Treatment Inventory of Costs in Patients with psychiatric disorders (TIC-P); VAS: Visual analogue scale; WHO: World Health Organization; WLC: Wait-list control group; WMH-ICS: WHO World Mental Health International College Student Initiative

Acknowledgements

The authors gratefully acknowledge the contribution of all participants, research assistants, therapists and all others who contributed to our study.

Funding

This study is funded by BARMER a German statutory health insurance company. The funding body had no role in the design, collection, analysis and interpretation of data and in the writing of the manuscript.

Availability of data and materials

The datasets used and/or analyzed during the current study are available from DDE.

Authors' contributions

DDE and HB obtained funding for this study. FK, DDE, TB and AS have contributed to the conception of the study design. FK drafted the manuscript, supervised by DDE. TB, AS, HB, MB, RA, RK, RB and PC contributed to the analysis and interpretation of data and critically revised the further writing of the manuscript. All authors read and approved the final manuscript and agreed to be accountable for all aspects of the work.

Ethics approval and consent to participate

This study was approved on 13.09.2016 by the Ethics Committee of the Friedrich-Alexander-Universität Erlangen-Nürnberg (ref. nr. 260_16 B, 13.09.2016). A written consent was obtained by all participants.

Consent for publication

Not applicable.

Competing interests

In the past 3 years, RCK received support for his epidemiological studies from Sanofi Aventis; was a consultant for Johnson & Johnson Wellness and Prevention, Sage Pharmaceuticals, Shire, Takeda; and served on an advisory board for the Johnson & Johnson Services Inc. Lake Nona Life Project. Kessler is a co-owner of DataStat, Inc., a market research firm that carries out healthcare research. The other authors declare that they have no competing interests. DDE reports to have received consultancy fees or served in the scientific advisory board from several companies such as Minddistrict, Sanofi, Lantern, Schön Kliniken, German health insurance companies (BARMER and Techniker Krankenkasse), and chambers of psychotherapists.
MB and DDE are stakeholders of the "Institute for Online Health Trainings", a company aiming to transfer scientific knowledge related to the present research into routine health care. HB reports to have received consultancy fees and fees for lectures or workshops from chambers of psychotherapists and training institutes for psychotherapists.
FK, TB, AS, PC, RB, RPA declare that they have no competing interests.

Publisher's Note

Author details

[1]Friedrich-Alexander-University Erlangen-Nürnberg (FAU), Nägelsbachstrasse 25a, 91052 Erlangen, Germany. [2]Department of Clinical Psychology and Psychotherapy, University of Bern, Bern, Switzerland. [3]Department of Clinical Psychology and Psychotherapy, University of Ulm, Ulm, Germany. [4]Department of Clinical, Neuro- and Developmental Psychology, Vrije University Amsterdam, Amsterdam, The Netherlands. [5]Research Group Psychiatry, Department of Neurosciences, KU Leuven University, Leuven, Belgium. [6]Department of Psychiatry, College of Physicians and Surgeons, Columbia University, New York, NY, USA. [7]Division of Clinical Developmental Neuroscience, Sackler Institute, New York, NY, USA. [8]Department for Health Care Policy, Harvard Medical School, Boston, MA, USA. [9]Department of Experimental Psychopathology and Psychotherapy, University of Zürich, Psychiatric University Hospital, Zürich, Switzerland.

Received: 28 May 2018 Accepted: 22 April 2019

References

1. Kessler R, Matthias A, Anthony J, De Graaf R. Lifetime prevalence and age-of-onset distributions of mental disorders in the World Health Organization's world mental health survey initiative. 2007. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2174588/. Accessed 25 Apr 2017.
2. Jacobi F, Höfler M, Strehle J, Mack S, Gerschler A, Scholl L, et al. Psychische Störungen in der Allgemeinbevölkerung. Studie zur Gesundheit Erwachsener in Deutschland und ihr Zusatzmodul psychische Gesundheit (DEGS1-MH). Nervenarzt. 2014;85:77–87.
3. Blanco C, Okuda M, Wright C, Hasin DS, Grant BF, Liu S-M, et al. Mental health of college students and their non–college-attending peers. Arch Gen Psychiatry. 2008;65:1429.
4. Tillfors M, Furmark T. Social phobia in Swedish university students: prevalence, subgroups and avoidant behavior. Soc Psychiatry Psychiatr Epidemiol. 2007;42:79–86. https://doi.org/10.1007/s00127-006-0143-2.
5. Mendlowicz MV, Stein MB. Quality of life in individuals with anxiety disorders. Am J Psychiatry. 2000;157:669–82.
6. Gültekin BK, Dereboy IF. The prevalence of social phobia, and its impact on quality of life, academic achievement, and identity formation in university students. Turk Psikiyatri Derg. 2011;22:150–8 http://www.ncbi.nlm.nih.gov/pubmed/21870304. Accessed 23 Jun 2017.
7. Gilles DM, Turk CL, Fresco DM. Social anxiety, alcohol expectancies, and self-efficacy as predictors of heavy drinking in college students. Addict Behav. 2006;31:388–98.
8. Olfson M, Guardino M, Struening E, Schneier FR, Hellman F, Klein DF. Barriers to the treatment of social anxiety. Am J Psychiatry. 2000;157:521–7.
9. Kessler RC. The impairments caused by social phobia in the general population: implications for intervention. Acta Psychiatr Scand. 2003;108:19–27. https://doi.org/10.1034/j.1600-0447.108.s417.2.x.
10. Magee WJ, Eaton WW, Wittchen H-U, McGonagle KA, Kessler RC. Agoraphobia, simple phobia, and social phobia in the National Comorbidity Survey. Arch Gen Psychiatry. 1996;53:159–68.
11. Wittchen H-U, Jacobi F. Size and burden of mental disorders in Europe—a critical review and appraisal of 27 studies. Eur Neuropsychopharmacol. 2005;15:357–76.
12. Wittchen H-U, Jacobi F, Rehm J, Gustavsson A. The size and burden of mental disorders and other disorders of the brain in Europe 2010. Eur Neuropsychopharmacol. 2011;21:655–79.
13. Chartier MJ, Hazen AL, Stein MB. Lifetime patterns of social phobia: a retrospective study of the course of social phobia in a nonclinical population. Depress Anxiety. 1998;7:113–21 http://www.ncbi.nlm.nih.gov/pubmed/9656091.
14. Acarturk C, Cuijpers P, van Straten A, de Graaf R. Psychological treatment of social anxiety disorder: a meta-analysis. Psychol Med. 2009;39:241. https://doi.org/10.1017/S0033291708003590.
15. Mayo-Wilson E, Dias S, Mavranezouli I, Kew K, Clark DM, Ades AE, et al. Psychological and pharmacological interventions for social anxiety disorder in adults: a systematic review and network meta-analysis. Lancet Psychiatry. 2014;1:368–76. https://doi.org/10.1016/S2215-0366(14)70329-3.
16. Wang PS, Berglund P, Olfson M, Pincus HA, Wells KB, Kessler RC. Failure and delay in initial treatment contact after first onset of mental disorders in the National Comorbidity Survey Replication. Arch Gen Psychiatry. 2005;62:603. https://doi.org/10.1001/archpsyc.62.6.603.
17. Runge AJ, Beesdo K, Lieb R, Wittchen H-U. How frequent is psychotherapy utilisation by adolescents and young adults with anxiety disorders? Verhaltenstherapie. 2008;18:26–34. https://doi.org/10.1159/000113890.
18. Rapee RM, Heimberg RG. A cognitive-behavioral model of anxiety in social phobia. Behav Res Ther. 1997;35:741–56 http://www.ncbi.nlm.nih.gov/pubmed/9256517.
19. Stangier U, Heidenreich T, Peitz M. Soziale Phobien : ein kognitiv-verhaltenstherapeutisches Behandlungsmanual. Weinheim: Beltz: mit CD-ROM; 2009.
20. King SA, Poulos ST. Using the Internet to Treat Generalized Social Phobia and Avoidant Personality Disorder. CyberPsychology {&} Behav. 1998;1:29–36. https://doi.org/10.1089/cpb.1998.1.29.
21. Berger T, Andersson G. Internetbasierte Psychotherapien: Besonderheiten und empirische Evidenz. PPmP - Psychother Psychosom Medizinische Psychol. 2009;59(03/04):159–70. https://doi.org/10.1055/s-0028-1090162.
22. Ebert DD, Van Daele T, Nordgreen T, Karekla M, Compare A, Zarbo C, et al. Internet- and Mobile-based psychological interventions: applications, efficacy, and potential for improving mental health. Eur Psychol. 2018;23:167–87. https://doi.org/10.1027/1016-9040/a000318.
23. Ebert DD, Cuijpers P, Muñoz RF, Baumeister H. Prevention of mental health disorders using internet- and mobile-based interventions: a narrative review and recommendations for future research. Front Psychiatry. 2017;8(AUG):116. https://doi.org/10.3389/fpsyt.2017.00116.
24. Griffiths F, Lindenmeyer A, Powell J, Lowe P, Thorogood M. Why are health care interventions delivered over the internet? A systematic review of the published literature. J Med Internet Res. 2006;8:e10.
25. Kampmann IL, Emmelkamp PMG, Morina N. Meta-analysis of technology-assisted interventions for social anxiety disorder. J Anxiety Disord. 2016;42:71–84. https://doi.org/10.1016/j.janxdis.2016.06.007.
26. Tillfors M, Carlbring P, Furmark T, Lewenhaupt S, Spak M, Eriksson A, et al. Treating university students with social phobia and public speaking fears: internet delivered self-help with or without live group exposure sessions. Depress Anxiety. 2008;25:708–17. https://doi.org/10.1002/da.20416.
27. Berger T, Caspar F, Richardson R, Kneubühler B, Sutter D, Andersson G. Internet-based treatment of social phobia: a randomized controlled trial comparing unguided with two types of guided self-help. Behav Res Ther. 2011;49:158–69. https://doi.org/10.1016/j.brat.2010.12.007.
28. Botella C, Gallego MJ, Garcia-Palacios A, Guillen V, Baños RM, Quero S, et al. An internet-based self-help treatment for fear of public speaking : a controlled trial. Cyberpsychol Behav Soc Netw. 2010;13. https://doi.org/10.1089/cyber.2009.0224.
29. Furmark T, Carlbring P, Hedman E, Sonnenstein A, Clevberger P, Bohman B, et al. Guided and unguided self-help for social anxiety disorder: randomised controlled trial. Br J Psychiatry. 2009;195:440–7. https://doi.org/10.1192/bjp.bp.108.060996.
30. Gallego MJ, Emmelkamp G, Maria P, van der Kooij M, Mees H. The effects of a Dutch version of an internet-based treatment program for fear of public speaking: a controlled study. Int J Clin Heal Psychol. 2011;11:459–72 http://www.redalyc.org/articulo.oa?id=33719289003. Accessed 29 Nov 2017.
31. Lopez GC, Botella C, Quero S, Gomez AR, Baños R. Telepsychology program to treat public-speaking anxiety among the Mexican population. 2014.
32. Titov N, Andrews G, Choi I, Schwencke G, Mahoney A. Shyness 3: randomized controlled trial of guided versus unguided internet-based CBT for social phobia. Aust New Zeal J Psychiatry. 2008;42:1030–40. https://doi.org/10.1080/00048670802512107.
33. Titov N, Andrews G, Choi I, Schwencke G, Johnston L. Randomized controlled trial of web-based treatment of social phobia without clinician guidance. Aust New Zeal J Psychiatry. 2009;43:913–9. https://doi.org/10.1080/00048670903179160.
34. Titov N, Andrews G, Schwencke G, Robinson E, Peters L, Spence J. Randomized controlled trial of internet cognitive Behavioural treatment for social phobia with and without motivational enhancement strategies. Aust New Zeal J Psychiatry. 2010;44:938–45. https://doi.org/10.3109/00048674.2010.493859.
35. Paganini S, Teigelkötter W, Buntrock C, Baumeister H. Economic evaluations of internet- and mobile-based interventions for the treatment and prevention of depression: a systematic review. J Affect Disord. 2018;225:733–55. https://doi.org/10.1016/j.jad.2017.07.018.
36. Ebert DD, Kählke F, Buntrock C, Berking M, Smit F, Heber E, et al. A health economic outcome evaluation of an internet-based mobile-supported stress management intervention for employees. Scand J Work Environ Health. 2018;44:171–82. https://doi.org/10.5271/sjweh.3691.
37. Donker T, Blankers M, Hedman E, Ljótsson B, Petrie K, Christensen H. Economic evaluations of Internet interventions for mental health: a systematic review. Psychol Med. 2015; AUGUST:1–20. https://doi.org/10.1017/S0033291715001427.
38. Hedman E, Andersson E, Ljótsson B, Andersson G, Rück C, Lindefors N. Cost-effectiveness of internet-based cognitive behavior therapy vs. cognitive behavioral group therapy for social anxiety disorder: results from a randomized controlled trial. Behav Res Ther. 2011;49:729–36. https://doi.org/10.1016/j.brat.2011.07.009.
39. Hedman E, El Alaoui S, Lindefors N, Andersson E, Ruck C, Ghaderi A, et al. Clinical effectiveness and cost-effectiveness of internet- vs. group-based cognitive behavior therapy for social anxiety disorder: 4-year follow-up of a randomized trial. Behav Res Ther. 2014;59:20–9.

40. Titov N, Andrews G, Johnston L, Schwencke G, Choi I. Shyness programme: longer term benefits, cost-effectiveness, and acceptability. Aust N Z J Psychiatry. 2009;43:36–44.
41. Weeks JW, Heimberg RG, Rodebaugh TL. The fear of positive evaluation scale: assessing a proposed cognitive component of social anxiety. J Anxiety Disord. 2008;22:44–55. https://doi.org/10.1016/j.janxdis.2007.08.002.
42. Weeks JW, Heimberg RG, Rodebaugh TL, Goldin PR, Gross JJ. Psychometric evaluation of the fear of positive evaluation scale in patients with social anxiety disorder. Psychol Assess. 2012;24:301–12. https://doi.org/10.1037/a0025723.
43. Hedman E, Andersson G, Ljótsson B, Andersson E, Rück C, Mörtberg E, et al. Internet-based cognitive behavior therapy vs. Cognitive behavioral group therapy for social anxiety disorder: a randomized controlled non-inferiority trial. PLoS One. 2011;6:e18001. https://doi.org/10.1371/journal.pone.0018001.
44. Weeks JW, Howell AN. The bivalent fear of evaluation model of social anxiety: further integrating findings on fears of positive and negative evaluation. Cogn Behav Ther. 2012;41:83–95. https://doi.org/10.1080/16506073.2012.661452.
45. Gilbert P. Evolutionary Models: Practical and Conceptual Utility for the Treatment and Study of Social Anxiety Disorder. The Wiley Blackwell Handbook of Social Anxiety Disorder. 2014;:24–52. doi:https://doi.org/10.1002/9781118653920.ch2.
46. Weeks JW, Jakatdar TA, Heimberg RG. Comparing and contrasting fears of positive and negative evaluation as facets of social anxiety. J Soc Clin Psychol. 2010;29:68–94. https://doi.org/10.1521/jscp.2010.29.1.68.
47. Weeks JW, Howell AN. Fear of Positive Evaluation: The Neglected Fear Domain in Social Anxiety. The Wiley Blackwell Handbook of Social Anxiety Disorder. 2014;:433–53. doi:https://doi.org/10.1002/9781118653920.ch20.
48. Goldin PR, Ziv M, Jazaieri H, Hahn K, Heimberg R, Gross JJ. Impact of cognitive behavioral therapy for social anxiety disorder on the neural dynamics of cognitive reappraisal of negative self-beliefs: randomized clinical trial. JAMA psychiatry. 2013;70:1048–56. https://doi.org/10.1001/jamapsychiatry.2013.234.
49. Fergus TA, Valentiner DP, McGrath PB, Stephenson K, Gier S, Jencius S. The fear of positive evaluation scale: psychometric properties in a clinical sample. J Anxiety Disord. 2009;23:1177–83. https://doi.org/10.1016/j.janxdis.2009.07.024.
50. Bruffaerts R, Mortier P, Kiekens G, Auerbach RP, Cuijpers P, Demyttenaere K, et al. Mental health problems in college freshmen: prevalence and academic functioning. J Affect Disord. 2018;225:97–103. https://doi.org/10.1016/j.jad.2017.07.044.
51. Mortier P, Demyttenaere K, Auerbach RP, Cuijpers P, Green JG, Kiekens G, et al. First onset of suicidal thoughts and behaviours in college. J Affect Disord. 2017;207:291–9 https://doi.org/10.1016/j.jad.2016.09.033.
52. Clark D, Wells A. A cognitive model of social phobia. New York: Guilford Press; 1995.
53. Boettcher J, Berger T, Renneberg B. Does a pre-treatment diagnostic interview affect the outcome of internet-based self-help for social anxiety disorder? A randomized controlled trial. Behav Cogn Psychother. 2012;40:513–28. https://doi.org/10.1017/S1352465812000501.
54. Berger T, Hohl E, Caspar F. Internetbasierte Therapie der sozialen Phobie: Ergebnisse einer 6-monate-katamnese. Zeitschrift für klinische Psychologie und Psychotherapie 2010; 39:217–21.
55. Schulz A, Stolz T, Berger T. Internet-based individually versus group guided self-help treatment for social anxiety disorder: protocol of a randomized controlled trial 2014. doi:https://doi.org/10.1186/1471-244X-14-115.
56. Berger T, Hohl E, Caspar F. Internet-based treatment for social phobia: a randomized controlled trial. J Clin Psychol. 2009;65:1021–35. https://doi.org/10.1002/jclp.20603.
57. Werner KH, Goldin PR, Ball TM, Heimberg RG, Gross JJ. Assessing emotion regulation in social anxiety disorder: the emotion regulation interview. J Psychopathol Behav Assess. 2011;33:346–54. https://doi.org/10.1007/s10862-011-9225-x.
58. Ebert DD, Buntrock C, Lehr D, Smit F, Riper H, Baumeister H, et al. Effectiveness of web- and mobile-based treatment of subthreshold depression with adherence-focused guidance. A single-blind randomised controlled trial. Behav Ther. 2017.
59. Ebert DD, Lehr D, Heber E, Riper H, Cuijpers P, Berking M. Internet- and mobile-based stress management for employees with adherence-focused guidance: efficacy and mechanism of change. Scand J Work Environ Health. 2016;42:382–94. https://doi.org/10.5271/sjweh.3573.
60. Zarski A-C, Lehr D, Berking M, Riper H, Cuijpers P, Ebert DD. Adherence to internet-based Mobile-supported stress management: a pooled analysis of individual participant data from three randomized controlled trials. J Med Internet Res. 2016;18:e146. https://doi.org/10.2196/jmir.4493.
61. Questback GmbH. Unipark. EFS Survey 2016. https://www.unipark.com/en/survey-software/.
62. Stangier U, Heidenreich T, Berardi A, Golbs U, Hoyer J. Die Erfassung sozialer Phobie durch die Social Interaction Anxiety Scale (SIAS) und die Social Phobia Scale (SPS). Z Klin Psychol Psychother. 1999;28:28–36. https://doi.org/10.1026//0084-5345.28.1.28.
63. Mattick RP, Clarke JC. Development and validation of measures of social phobia scrutiny fear and social interaction anxiety11Editor's note: this article was written before the development of some contemporary measures of social phobia, such as the social phobia and anxiety Inve. Behav Res Ther. 1998;36:455–70. https://doi.org/10.1016/S0005-7967(97)10031-6.
64. Heinrichs N, Hahlweg K, Fiegenbaum W, Frank M, Schroeder B, von Witzleben I. Validität und Reliabilität der social interaction anxiety scale (SIAS) und der social phobia scale (SPS). Verhaltenstherapie. 2002;12:26–35. https://doi.org/10.1159/000056690.
65. Wittchen H-U, Wunderlich U, Gruschwitz S, Zaudig M. SKID I. Strukturiertes Klinisches Interview für DSM-IV. Achse I: Psychische Störungen. Interviewheft und Beurteilungsheft. Eine deutschsprachige, erweiterte Bearb. d. amerikanischen Originalversion des SKID I. Göttingen: Hogrefe; 1997.
66. Hautzinger M, Keller F, Kühner C. Beck depressions-Inventar (BDI-II). Frankfurt am Main: Harcourt Test Services; 2006.
67. Franke G. BSI, Brief Symptom Inventory von L. R. Derogatis (Kurzform der SCL-90-R) - deutsches Manual. Beltz Test GmbH. 2000.
68. Schlarb A, Hautzinger M. Klinisch-psychiatrische Ratingskalen für das Kindes- und Jugendalter. Göttingen: Hogrefe; 2011.
69. Stangier U, Heidenreich T. Die Liebowitz Soziale Angst-Skala (LSAS). Göttingen: Hogrefe; 2003.
70. Liebowitz M. Social Phobia. Mod Probl Pharmacopsychiatry. 1987;22:141–73.
71. Horowitz L, Rosenberg SE, Bear BA, Ureno G, Villasenor VS. Inventory of interpersonal problems: psychometric properties and clinical applications. J Consult Clin Psychol. 1988;56:885–92 http://psycnet.apa.org/journals/ccp/56/6/885/. Accessed 30 May 2017.
72. Horowitz L, Strauß B, Kordy H. Inventar zur Erfassung interpersonaler Probleme. Deutsche Version. Manual (2., überarbeitete und neu normierte Auflage). Göttingen: Beltz Test GmbH; 2000.
73. Weeks JW, Heimberg RG, Rodebaugh TL, Norton PJ. Exploring the relationship between fear of positive evaluation and social anxiety. J Anxiety Disord. 2008;22:386–400. https://doi.org/10.1016/j.janxdis.2007.04.009.
74. Weeks JW. The disqualification of positive social outcomes scale: a novel assessment of a long-recognized cognitive tendency in social anxiety disorder. J Anxiety Disord. 2010;24:856–65. https://doi.org/10.1016/j.janxdis.2010.06.008.
75. Richardson J, Iezzi A, Khan MA, Maxwell A. Validity and reliability of the assessment of quality of life (AQoL)-8D multi-attribute utility instrument. Patient - Patient-Centered Outcomes Res. 2014;7:85–96. https://doi.org/10.1007/s40271-013-0036-x.
76. EuroQol Group. EuroQol--a new facility for the measurement of health-related quality of life. Health Policy. 1990;16:199–208 doi:10109801.
77. Herdman M, Gudex C, Lloyd A, Janssen M, Kind P, Parkin D, et al. Development and preliminary testing of the new five-level version of EQ-5D (EQ-5D-5L). Qual Life Res. 2011;20:1727–36. https://doi.org/10.1007/s11136-011-9903-x.
78. Bouwmans C, De Jong K, Timman R, Zijlstra-Vlasveld M, Van der Feltz-Cornelis C, Tan Swan S, et al. Feasibility, reliability and validity of a questionnaire on healthcare consumption and productivity loss in patients with a psychiatric disorder (TiC-P). BMC Health Serv Res. 2013;13:217. https://doi.org/10.1186/1472-6963-13-217.
79. Krauth C. Methoden der Kostenbestimmung in der gesundheitsökonomischen Evaluation. Gesundheitsökonomie Qual. 2010;15:251–9. https://doi.org/10.1055/s-0029-1245680.
80. Bock J-O, Bowles D, Brettschneider C, Greiner W, Holle R, König H-H, et al. Standardisierte Bewertungssätze aus gesellschaftlicher Perspektive für die gesundheitsökonomische Evaluation. 1st ed. Baden-Baden: Nomos Verlagsgesellschaft mbH & Co. KG; 2015. https://doi.org/10.5771/9783845260754.
81. Buntrock C, Berking M, Smit F, Lehr D, Nobis S. Preventing Depression in Adults With Subthreshold Depression : Health-Economic Evaluation

Alongside a Pragmatic Randomized Controlled Trial of a Web-Based Intervention Corresponding Author : 2017;19:1–16.
82. Bundesministerium für Bildung und Forschung. Welche Bedarfssätze sieht das BAföG vor? 2018. https://www.bafög.de/de/welche-bedarfssaetze-sieht-das-bafoeg-vor--375.php. Accessed 2018-02-01 (Archived by WebCite® at http://www.webcitation.org/70cTqTjLg).
83. Schmidt J, Lamprecht F, Wittmann W. Zufriedenheit mit der stationären Versorgung. Entwicklung eines Fragebogens und erste Validitätsuntersuchungen. Psychother Psychosom. 1989. https://www.gfqg.de/assessment/zuf-8.html. Accessed 30 May 2017.
84. Boß L, Lehr D, Reis D, Vis C, Riper H, Berking M, et al. Reliability and validity of assessing user satisfaction with web-based health interventions. J Med Internet Res. 2016;18:e234. https://doi.org/10.2196/jmir.5952.
85. Devilly GJ, Borkovec TD. Psychometric properties of the credibility/expectancy questionnaire. J Behav Ther Exp Psychiatry. 2000;31:73–86. https://doi.org/10.1016/S0005-7916(00)00012-4.
86. European Commission. European Credit Transfer and Accumulation System (ECTS). 2017. https://ec.europa.eu/education/resources-and-tools/european-credit-transfer-and-accumulation-system-ects_en. Accessed: 2017-12-05. (Archived by WebCite® at http://www.webcitation.org/6vUFF2q8f).
87. Erdfelder E, Faul F, Buchner A. GPOWER: A general power analysis program. Behav Res Methods, Instruments, Comput. 1996.
88. Altman D. Better reporting of randomised controlled trials: the CONSORT statement. BMJ Br Med J. 1996; https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2352018/. Accessed 6 Jun 2017.
89. Little RJA, Rubin DB. Statistical analysis with missing data. 2nd ed. Hoboken NJ: Wiley; 2002.
90. Schafer JL, Reid N, Cox D, Keiding N, Louis T, Tong H, et al. Analysis of incomplete multivariate data. New York, NY, US: Chapman and Hall/CRC; 1997.
91. Jacobson NS, Truax P. Clinical significance: a statistical approach to defining meaningful change in psychotherapy research. J Consult Clin Psychol. 1991;59:12–9.
92. Johnson PO, Fay LC. The Johnson-Neyman technique, its theory and application. Psychometrika. 1950;15:349–67. https://doi.org/10.1007/BF02288864.
93. Ramsey SD, Willke RJ, Glick H, Reed SD, Augustovski F, Jonsson B, et al. Cost-effectiveness analysis alongside clinical trials II—an ISPOR good research practices task force report. Value Heal. 2015;18:161–72. https://doi.org/10.1016/j.jval.2015.02.001.
94. Husereau D, Drummond M, Petrou S, Carswell C, Moher D, Greenberg D, et al. Consolidated health economic evaluation reporting standards (CHEERS) statement. Eur J Health Econ. 2013;14:367–72. https://doi.org/10.1007/s10198-013-0471-6.
95. Spek V, Cuijpers P, Nyklicek I, Riper H, Keyzer J, Pop V. Internet-based cognitive behaviour therapy for symptoms of depression and anxiety: a meta-analysis. Psychol Med. 2007;37:319. https://doi.org/10.1017/S0033291706008944.
96. Andersson G, & Cuijpers P. Internet-based and other computerized psychological treatments for adult depression: a meta-analysis. Cognitive behaviour therapy. 2009;38(4):196–205.
97. Nordin S, Carlbring P, Cuijpers P, Andersson G. Expanding the limits of Bibliotherapy for panic disorder: randomized trial of self-help without support but with a clear deadline. Behav Ther. 2010;41:267–76. https://doi.org/10.1016/j.beth.2009.06.001.
98. Titov N, Dear BF, Johnston L, Lorian C, Zou J, Wootton B, et al. Improving adherence and clinical outcomes in self-guided internet treatment for anxiety and depression: randomised controlled trial. PLoS One. 2013;8:e62873. https://doi.org/10.1371/journal.pone.0062873.
99. Andersson G, Titov N. Advantages and limitations of internet-based interventions for common mental disorders. World Psychiatry. 2014;13:4–11. https://doi.org/10.1002/wps.20083.
100. Ebert DD, Baumeister H. Internet-based self-help interventions for depression in routine care. JAMA Psychiatry. 2017;74:852. https://doi.org/10.1001/jamapsychiatry.2017.1394.
101. Titov N, Andrews G, Kemp A, Robinson E. Characteristics of adults with anxiety or depression treated at an internet clinic: comparison with a national survey and an outpatient clinic. PLoS One. 2010;5:e10885. https://doi.org/10.1371/journal.pone.0010885.
102. van den Brink M, van den Hout WB, Stiggelbout AM, Putter H, van de Velde CJH, Kievit J. Self-reports of health-care utilization: diary or questionnaire? Int J Technol Assess Health Care. 2005;21:298–304. https://doi.org/10.1017/S0266462305050397.
103. Scaini S, Belotti R, Ogliari A, Battaglia M. A comprehensive meta-analysis of cognitive-behavioral interventions for social anxiety disorder in children and adolescents. J Anxiety Disord. 2016;42:105–12. https://doi.org/10.1016/j.janxdis.2016.05.008.

3.2 Article 2: Efficacy of an IMI for Students with SAD

Authors:	Fanny Kählke, Thomas Berger, Ava Schulz, Harald Baumeister, Matthias Berking, Randy P. Auerbach, Ronny Bruffaerts, Pim Cuijpers, Ronald C. Kessler & David D. Ebert
Title:	Efficacy of an unguided internet-based self-help intervention for social anxiety disorder in university students: A randomized controlled trial
Journal:	*International Journal of Methods in Psychiatric Research*, Vol. 28, No. e1766 (2019) https://onlinelibrary.wiley.com/doi/epdf/10.1002/mpr.1766
DOI:	https://doi.org/10.1002/mpr.1766
Trial register:	https://www.drks.de/DRKS00011424

Social anxiety disorder (SAD) is prevalent and often remains untreated leading to adverse consequences among students. Internet- and mobile-based self-help interventions (IMIs) can overcome treatment barriers. This randomized controlled trial examined the efficacy of an unguided IMI (StudiCare soziale Ängste) targeting SAD among students. The intervention includes 9 modules based on the cognitive-behavioral approach by Clark and Wells (1995). The IMI is unguided offering no support by a therapist but standardized automatic messages to increase adherence. In this trial 200 students aged 18 years or above showing a primary diagnosis of SAD (Social Phobia Scale [SPS] ≥ 21 or Social Interaction Anxiety [SIAS] ≥ 32) were randomly assigned to either or an intervention group (IG) (n = 100) or to a waitlist control (WLC) (n = 100) with unrestricted access to treatment as usual. The primary outcome of this study were SAD symptoms at post-treatment, 10 weeks after randomization. Secondary outcomes were, among others, diagnostic status, costs, quality of life, depressive symptomatology, and fear of positive evaluation. Diagnostic status was assessed through Structured Clinical Interview for DSM-4 Axis I Disorders (SCID-I). Participants were on average 27 years old (26.7, standard deviations [SD] = 6.34), female (62%) full-time students (85%). One third of the participants (34%) had some experience with psychotherapy. All characteristics were balanced across groups and drop-out was relatively low (IG: 9% vs. WLC: 6%). On average, 5.18 (SD = 2.65) out of 9 modules were completed by the participants. Client satisfaction was high (83%). The reduction of SAD symptoms at post-test indicated moderate to large effect sizes in favor of the IMI compared with WLC (SPS: d = 0.76; SIAS: d = 0.55, $p < 0.001$). The analysis of covariance generated significant lower scores for the IMI compared with WLC (analysis of covariance [ANCOVA]: SPS: $F(1, 197) = 94.65$, $p < 0.001$; ANCOVA SIAS: $F(1, 197) = 122.51$, $p < 0.001$). Effects on all secondary outcomes were significant and in favor of the IMI. The intervention proved

effective in reducing SAD symptoms in university students and may provide an alternative treatment option to reach affected students at an early stage.

The manuscript was submitted in July 2018, revised in November 2018, accepted in December 2018, and published in January 2019 and in June 2019 as part of a special issue of the WHO World Mental Health International College Student (WMH-ICS) initiative in the *International Journal of Methods in Psychiatric Research*. This is an international open access journal that publishes high-standard original research related to mental and behavioral disorders. The article is published under the copyright transfer agreement that allows for it to be reused in another publication if "the final Published Version or parts thereof for any publication authored or edited by the Contributor (excluding journal articles) where such re-used material constitutes less than half of the total material in such publication" and it is appropriately cited and linked to the publisher.

Contribution: Fanny Kählke was the principal investigator and author of the published article. David D. Ebert and Harald Baumeister obtained funding for this study as part of the StudiCare project. Thomas Berger developed the evaluated intervention. Fanny Kählke supported by David D. Ebert, Thomas Berger, Ava Schulz developed the conception of the study design. Fanny conducted the study, prepared, and analyzed the dataset. She wrote the published article and was supervised by David D. Ebert. All co-authors read, critically revised, and finally approved the published article.

Received: 1 July 2018 | Revised: 25 November 2018 | Accepted: 1 December 2018

DOI: 10.1002/mpr.1766

SPECIAL ISSUE

WILEY

Efficacy of an unguided internet-based self-help intervention for social anxiety disorder in university students: A randomized controlled trial

Fanny Kählke[1] | Thomas Berger[2] | Ava Schulz[3] | Harald Baumeister[4] | Matthias Berking[1] | Randy P. Auerbach[5,6] | Ronny Bruffaerts[7] | Pim Cuijpers[8] | Ronald C. Kessler[9] | David Daniel Ebert[1]

[1]Department of Clinical Psychology and Psychotherapy, University of Erlangen–Nuremberg, Erlangen, Germany

[2]Department of Clinical Psychology and Psychotherapy, University of Bern, Bern, Switzerland

[3]Department of Experimental Psychopathology and Psychotherapy, University of Zürich, Psychiatric University Hospital, Zürich, Switzerland

[4]Department of Clinical Psychology and Psychotherapy, University of Ulm, Ulm, Germany

[5]Department of Psychiatry, College of Physicians and Surgeons, Columbia University, New York City, New York, USA

[6]Division of Clinical Developmental Neuroscience, Sackler Institute, New York City, New York, USA

[7]Research Group Psychiatry, Department of Neurosciences, KU Leuven University, Leuven, Belgium

[8]Department of Clinical, Neuro, and Developmental Psychology, Vrije Universiteit Amsterdam, Amsterdam, The Netherlands

[9]Department for Health Care Policy, Harvard Medical School, Boston, Massachusetts, USA

Correspondence
Fanny Kählke, Department of Clinical Psychology and Psychotherapy, Friedrich–Alexander University Erlangen–Nuremberg, Nägelsbachstraße 25a, 91052 Erlangen, Germany.
Email: fanny.kaehlke@fau.de

Funding information
BARMER

Abstract

Objectives: Internet- and mobile-based interventions (IMIs) offer the opportunity to deliver mental health treatments on a large scale. This randomized controlled trial evaluated the efficacy of an unguided IMI (StudiCare SAD) for university students with social anxiety disorder (SAD).

Methods: University students (N = 200) diagnosed with SAD were randomly assigned to an IMI or a waitlist control group (WLC) with full access to treatment as usual. StudiCare SAD consists of nine sessions. The primary outcome was SAD symptoms at posttreatment (10 weeks), assessed via the Social Phobia Scale (SPS) and the Social Interaction Anxiety Scale (SIAS). Secondary outcomes included depression, quality of life, fear of positive evaluation, general psychopathology, and interpersonal problems.

Results: Results indicated moderate to large effect sizes in favor of StudiCare SAD compared with WLC for SAD at posttest for the primary outcomes (SPS: d = 0.76; SIAS: d = 0.55, p < 0.001). Effects on all secondary outcomes were significant and in favor of the intervention group.

Conclusion: StudiCare SAD has proven effective in reducing SAD symptoms in university students. Providing IMIs may be a promising way to reach university students with SAD at an early stage with an effective treatment.

KEYWORDS

internet-based treatment, social anxiety disorder, unguided self-help, university students

1 | INTRODUCTION

Social anxiety disorder (SAD) is the most common anxiety disorder in the general population (Kessler, Chiu, Demler, & Walters, 2005). Prevalence estimates for SAD in university students show a wide range from 3.4% (12 months) in the United States (Blanco et al., 2008) to 16.1% (point prevalence) in Sweden (Tillfors & Furmark, 2007).

University students with SAD face a number of adverse effects including problems with identity formation (Gültekin & Dereboy, 2011), increased consumption of alcohol (Gilles, Turk, & Fresco, 2006), higher levels of suicidal ideation (Olfson, 2000), and lower quality of life (Mendlowicz, 2000). In addition, emotional distress due to SAD triggers dysfunctional avoidance strategies (Tillfors & Furmark, 2007), which are associated with underachievement and may lead to university dropout. The resulting lower qualification and social impairment (Kessler, 2003; Magee, Eaton, Wittchen, McGonagle, & Kessler, 1996) may subsequently lead to a high economic burden for those affected as well as for society at large. Thus, treatment of SAD is of interest to the public health care system and health services in and outside of the university setting (Wittchen & Jacobi, 2005; Wittchen, Jacobi, Rehm, & Gustavsson, 2011), particularly as SAD can manifest as a chronic condition when untreated (Chartier, Hazen, & Stein, 1998).

However, only a fraction of those in need (Runge, Beesdo, Lieb, & Wittchen, 2008; Wang et al., 2005) receive help. Reasons for this unmet need include shortage in available clinicians and fear of stigmatization. Furthermore, the fear of negative evaluation (FNE; Rapee & Heimberg, 1997; Stangier, Heidenreich, & Peitz, 2009), the expectation that others might judge one's behavior as embarrassing (Kessler, 2003; King & Poulos, 1998), a key feature of SAD, prevents university students from seeking professional advice (Kessler, 2003; King & Poulos, 1998).

Internet- and mobile-based interventions (IMIs) are a promising strategy to overcome treatment barriers by offering a low-access threshold, anonymous, flexible, and effective treatment option (Ebert, Cuijpers, Muñoz, & Baumeister, 2017; Griffiths, Lindenmeyer, Powell, Lowe, & Thorogood, 2006). IMIs have been shown to be effective in the treatment of a broad range of disorders (Ebert, Van Daele, et al., 2018b). The latest systematic review on IMIs for SAD found a mean standardized effect size of g = 0.84 (0.72–0.97) compared with untreated control groups and g = 0.38 (0.13–0.62) compared with active control conditions (Kampmann, Emmelkamp, & Morina, 2016).

Most studies to date that targeted SAD evaluated guided IMIs. However, once developed, costs of IMIs are substantially linked to professional guidance time, which clearly limits their possible reach and consequently lowers the potential to reduce the negative consequences of SAD at population level. Thus, in light of technological developments that allow them to mimic some functions of human support, unguided IMIs have received more attention. The most recent meta-analysis found an average effect of g = 0.78 (95% confidence interval [CI] [0.50, 1.05]) for unguided IMIs compared with passive controls (n = 8) and of g = 0.19 (95% CI [−0.08, 0.46]) compared with active conditions (n = 7; Kampmann et al., 2016).

However, effect sizes of unguided treatment vary widely (95% CI [0.28, 1.47]; Berger et al., 2011; Botella et al., 2010; Furmark et al., 2009; Gallego, Emmelkamp, Maria, van der Kooij, & Mees, 2011; Lopez, Botella, Quero, Gomez, & Baños, 2014; Titov et al., 2010; Titov, Andrews, Choi, Schwencke, & Johnston, 2009; Titov, Andrews, Choi, Schwencke, & Mahoney, 2008) and high dropout >40% at posttreatment (Botella et al., 2010; Gallego et al., 2011). Therefore, additional research is needed to investigate the efficacy of unguided IMIs as treatment of SAD.

We are aware of two studies that evaluated internet-based cognitive behavioral therapy (iCBT) for SAD in university students. A small open trial (n = 38) that delivered PDFs with self-help material and offered minimal contact with a psychotherapist resulted in large pre–post within-group effects (Social Interaction Anxiety Scale [SIAS]: d = 0.81; Social Phobia Scale [SPS]: d = 1.18) for both the iCBT group and the iCBT group with additional in vivo group exposure (Tillfors et al., 2008). Another unguided web-based intervention that was personalized to each user's symptoms yielded smaller pre–post effect sizes in a non-clinical sample of psychology students (e.g., SIAS: d = 0.72; McCall, Richardson, Helgadottir, & Chen, 2018).

Although the efficacy of cognitive behavioral therapy (CBT) in the treatment of SAD is well documented (Kampmann et al., 2016), there is still room for improvement. Recent findings suggest that FNEs are a central feature of SAD and document a strong link between SAD and the fear of positive evaluation (FPE; Hedman et al., 2011; Weeks, Heimberg, & Rodebaugh, 2008; Weeks, Heimberg, Rodebaugh, Goldin, & Gross, 2012). According to Weeks and Howell's (2012) bivalent fear of evaluation model of social phobia, fear of evaluation in general is the core component of SAD, including not only FNE but also FPE. Empirical evidence shows that FPE and FNE are related but distinct factors contributing to social anxiety, with FPE explaining a unique and independent proportion of variance in the fear of social interactions (Weeks, Jakatdar, & Heimberg, 2010). Even though established treatments for SAD do not address FPE directly, there is evidence that CBT can reduce FPE, albeit with smaller effect sizes compared with FNE (Weeks et al., 2012). Neglecting this component of SAD in the treatment may impede treatment progress, such as when clients still feel anxious after successful exposures that received positive feedback (Weeks & Howell, 2014). Even though research has shown that FPE is sensitive to CBT (Fergus et al., 2009), to our knowledge, no intervention exists that systematically addresses this as a treatment component of SAD. Thus, the intervention used in our study was enhanced by one module on FPE.

The current study evaluated whether an unguided internet-based intervention complemented by one module on FPE is effective in treating SAD in university students when compared with a waitlist control group (WLC). This study is part of the recently launched World Health Organization World Mental Health Surveys International College Student Project (WMH-ICS; www.hcp.med.harvard.edu/wmh/college_student_survey.php; Bruffaerts et al., 2018; Mortier et al., 2017). The WMH-ICS was initiated to obtain accurate longitudinal data on the prevalence and correlates of mental disorders among university students, assess unmet needs for treatment, evaluate a wide range of interventions (a number of them developed in the context of WMH-ICS) to prevent and treat these disorders, and develop precision medicine clinical decision support tools to match the right students to the most appropriate treatments.

2 | METHODS

2.1 | Design and procedure

Using a two-arm randomized controlled design, N = 200 participants were randomly allocated (block size of 8, varying ratio) to an internet-based unguided CBT (n = 100) or to a 6-month WLC group (n = 100). Both groups had full access to treatment as usual. Randomization was performed using an internet-based randomization program (Randlist) and carried out by an independent researcher not otherwise involved in the study. All questionnaires were assessed online at baseline (T0), 10 weeks (T1, posttreatment), and 6 months (T2) after randomization. The WLC group received access to the intervention following T2. In this study, we only report pretreatment and posttreatment data. The trial was registered at the German Clinical Trials Register (DRKS00011424). More details on the study design can be found in the study protocol (Kählke et al., 2018). All procedures involved in the study were consistent with the generally accepted standards of ethical practice and were approved by the ethical committee of the University of Erlangen–Nuremberg (reference number 260_16 B, 13.09.2016).

2.2 | Participants

Participants had to be at least 18 years of age, enrolled as university students, scoring above predefined cutoff scores on the SPS (>21) or SIAS (>32), and meeting diagnostic criteria of SAD according to the Structured Clinical Interview for DSM-IV Axis I Disorders. The interviews were conducted by trained interviewers via telephone (Rohde, Lewinsohn, & Seeley, 1997). Interrater reliability was evaluated in 20% of randomly selected cases. Cohen's kappa was κ = 0.78, which indicates good agreement across raters (Landis & Koch, 1977).

We excluded applicants who were either at risk of suicide (Beck Suicide Item > 1) or receiving psychotherapy at the time of entering the study or had a known diagnosis of a psychotic, bipolar, or another severe mental disorder. Prescription medications for anxiety and depression lead to an exclusion if the dosage had changed within 1 month before the beginning of the study. Participants were recruited in Germany, Austria, and Switzerland from January 2017 to February 2018 primarily through circular e-mails sent to enrolled students at a number of German, Austrian, and Swiss universities.

2.3 | Intervention

The intervention is based on the cognitive behavioral treatment model for social phobia by Clark and Wells (1995). This model has been shown to be efficacious in previous studies in general population samples (Berger et al., 2011; Berger, Hohl, & Caspar, 2009, 2010; Boettcher, Berger, & Renneberg, 2012; A. Schulz et al., 2016; Stolz et al., 2018). The original intervention was specifically adapted to the university setting, for example, by providing case examples of socially anxious students. The intervention consisted of nine text-based sessions, various exercises (e.g., attention training), and diaries (such as a diary aimed to identify and challenge negative thoughts). Participants were asked to work on one session weekly, to revise the exercises, and to fill in the diaries. The approximate time required to complete one session was 60 min plus the time required to implement treatment strategies in their daily life routine.

The first three intervention sections are composed of motivational enhancement (Session 1), psycho-education (Session 2), and identification and modification of negative thoughts through a thought diary (Session 3). The fourth session consists of a module not in the original Clark and Wells model that teaches participants how to identify and modify FPE-related cognitions (Session 4). This module provides information on the definition and etiology of FPE regarding the bivalent fear of evaluation model (Weeks & Howell, 2012), the evolutionary model (Gilbert, 2014), and FPE-related cognitive strategies such as the disqualification of positive social outcomes. Identification and modification of FPE-related cognitions as well as perceived costs and advantages of positive evaluation are supported by a thought diary and complemented by exercises that facilitate self-compassion and the experience and acceptance of positive emotions, both of which have been linked to a reduction of FPE (Werner, Goldin, Ball, Heimberg, & Gross, 2011). In Sessions 5–7, participants are then introduced to exercises to reduce self-focused attention, including behavioral experiments such as in vivo exposures. Session 8 includes information about healthy lifestyle (e.g., sports and nutrition) and conveyed problem solving skills. Finally, Session 9 provides strategies to maintain the acquired skills and to prepare for relapses.

Although the intervention does not include any therapeutic guidance, participants receive standardized automatic messages aiming to promote adherence. Adherence reminders follow procedures used in a number of previously conducted studies (Ebert et al., 2016; Ebert, Buntrock, et al., 2018; Zarski et al., 2016) consisting of one positive reinforcement per session completion and one automatic reminder if participants do not log into the platform for more than one week. These automated reminders contain standardized motivational messages that encourage participants to continue to work with the program. A more detailed description of the StudiCare SAD can be found in the protocol of the trial (Kählke et al., 2018).

2.4 | Primary outcome measures

The primary outcome measures assess SAD symptoms with the SPS and the SIAS (Stangier, Heidenreich, Berardi, Golbs, & Hoyer, 1999). These two self-report questionnaires complement one another and are usually administered together. The SIAS assesses more general fears of social interaction (e.g., "I tense up if I meet an acquaintance in the street"), whereas the SPS focuses on fears of being judged by others during daily activities (e.g., "I become anxious if I have to write in front of others."). Each scale consists of 20 items rated on a 5-point Likert scale (0 = "not at all" to 4 = "extremely"). These two measures have been found to be valid, reliable, and useful for clinical and research purposes (Mattick & Clarke, 1998). Cronbach's α for the SIAS and SPS ranges from 0.90 to 0.94 (Heinrichs et al., 2002). In the present study, Cronbach's α at T1 was 0.91 for the SPS and 0.92 for the SIAS.

2.5 | Secondary outcome measures

Fear of positive social feedback was assessed using the Fear of Positive Evaluation Scale (FPES; Weeks, Heimberg, Rodebaugh, & Norton, 2008). The FPES is a self-report instrument, which consists of 10 items and has shown good psychometric properties in clinical and healthy samples (Fergus et al., 2009; Weeks, Heimberg, Rodebaugh, & Norton, 2008). The disqualification of positive social outcomes is a cognitive strategy that has been related to FPE (Weeks, Heimberg, Rodebaugh, & Norton, 2008; Weeks & Howell, 2012). This cognitive tendency is assumed to represent a mental safety behavior in the context of FPE and was measured using the Disqualification of Positive Social Outcomes Scale (DPSOS; Weeks, 2010). The DPSOS comprises 13 items and measures disqualification of positive outcomes towards other-oriented and self-oriented attributions. Cronbach's α in the current sample for FPE was 0.78, and for DPSOS, it was 0.91.

Depression severity was assessed using the Beck Depression Inventory II (Hautzinger, Keller, & Kühner, 2006). The scale consists of 21 items each rated on a 4-point Likert scale. Prior research has shown high reliability and validity in SAD clients (Berger et al., 2011). Cronbach's α in the present study was 0.89.

General psychopathology was assessed using the Brief Symptom Inventory, which spans nine dimensions, including insecurity in social situations, anxiety, depressiveness, and compulsivity (Franke, 2000). The Brief Symptom Inventory assesses symptoms within the past week and has shown robust psychometric properties (Schlarb & Hautzinger, 2011). Cronbach's α in the current sample was 0.96.

The Liebowitz Social Anxiety Scale (Liebowitz, 1987; Stangier & Heidenreich, 2003) assesses self-reported fear and avoidance in 24 different situations. Thirteen of the situations relate to performance and the remaining items to situations within the context of social interactions. Prior research has shown good to excellent reliability and validity (Stangier & Heidenreich, 2003). In this study, Cronbach's α was 0.95.

Difficulties in interpersonal behavior and causes of relational distress as indicated assertiveness and passivity of participants were assessed using the Inventory of Interpersonal Problems. The instrument has eight dimensions and shown adequate psychometric properties (Horowitz, Rosenberg, Baer, Ureño, & Al, 1988; Horowitz, Strauß, & Kordy, 2000). Cronbach's α in the present study was 0.94.

The Assessment of Quality of Life (AQoL; Richardson, Iezzi, Khan, & Maxwell, 2014) measured quality of life. The AQoL-8D comprises 35 items on eight dimensions (independent living, pain, senses, mental health, happiness, coping, relationships, and self-worth) and allows for the calculation of separate sum scores for each dimension. The AQoL is a reliable and valid instrument (Richardson et al., 2014; Cronbach's α = 0.96). In this sample α was 0.93.

The German Client Satisfaction Questionnaire (Schmidt, Lamprecht, & Wittmann, 1989) adapted to the online training context was administered to examine the acceptance of internet-based interventions and global client satisfaction on the intervention (Boß et al., 2016).

2.6 | Sample size calculation

The study was powered to detect small to medium effect sizes of d = 0.4 between the conditions in the intention-to-treat (ITT) analysis, using a one-sided test, with 80% power, adjusted for multiple testing due to two primary outcome tests. Hence, 100 participants were included per condition.

2.7 | Statistical analyses

All analyses are reported according to the Consolidated Standards of Reporting Trials statement (K. F. Schulz, Altman, & Moher, 2010) using ITT procedures. Additionally, study completer, that is, including only those that provided data at follow-up, were reported as sensitivity analysis. Analyses were performed using IBM SPSS version 25 (IBM SPSS, 2017). Multiple imputation using a Markov chain Monte Carlo multivariate imputation algorithm was used to handle missing data (Little & Rubin, 2002). Ten single estimations of the missing values were calculated based on the valid data for all available data at all assessment points (T0 and T1).

The intervention group (IG) and WLC were compared at 10 weeks (T1) using analysis of covariance (ANCOVA) with baseline levels as covariates. The primary outcome analyses were adjusted for multiple testing; hence, α was set at <0.025 for the primary outcome tests and <0.05 for all other tests. Cohen's d with 95% CIs was calculated based on the imputed dataset by comparing the means and *SD*s of the IG and WLC groups at posttest. According to Cohen (1988), d = 0.2 can be considered a small effect, d = 0.5 a medium effect, and d = 0.8 a large effect.

To determine the numbers of participants achieving a reliable, positive outcome, we coded participants as responders or non-responders according to the widely used Reliable Change Index of Jacobson and Truax (1991) using the following formula: 1.96 × *SD* × sqrt(2) × sqrt(1 − rel). Therefore, we used the standard deviation of the whole sample at T0 (SD_{SPS} = 12.68, SD_{SIAS} = 12.16) and the retest reliability of the SPS (r_{tt} = 0.96) and SIAS (r_{tt} = 0.92) according to the test authors (Stangier et al., 1999). The participants were defined as having reliably changed if their SPS score differed more than (−)7.03 points and their SIAS score more than (−)9.53 points from T0 to T1. To investigate potential negative effects on individual level, we also calculated the number of participants that displayed a reliable symptom deterioration from baseline to posttreatment (+7.03) using the Reliable Change Index.

Participants were rated as symptom-free if they scored 17 or below on the SPS and 26 or below on the SIAS (Stangier et al., 1999). Additionally, the numbers needed to treat (NNT), indicating the number of participants that have to be treated to generate one additional treatment response/symptom-free status as compared with the control group, were calculated (Altman, 1998; Cook & Sackett, 1995).

3 | RESULTS

3.1 | Participants

A total of 603 individuals were screened for eligibility, and 387 were excluded primarily because they either scored below the cutoff (109/603) or because of a lack of informed consent/baseline (175/603). Subsequently, 16 participants were excluded due to no SAD diagnosis (n = 10), other mental disorders that require treatment (n = 5), and suicidal ideation (n = 16). Overall, 7.5% (n = 15) of participants did not provide data at T1. No significant differences were found between the IG (n = 9, 9%) and WLC (n = 6, 6%) with regard to missing data, $\chi^2(1) = 0.649$, $p = 0.421$. The study flow is illustrated in Figure 1.

Baseline socio-demographic and clinical characteristics were balanced across groups and are displayed in Table 1. The average age of the participants was 26.70 years (SD = 6.34). The sample was primarily female (124/200, 62%) and consisted mostly of full-time students (n = 170, 85%), who were related to medical fields (n = 77, 39.1%). Half of them were married or in a relationship (n = 102, 51.0%). Having received psychotherapy in the past was endorsed by 68 persons (34.0%). Table 2 summarizes all means and SDs for all outcome measures.

The most common reason that participants indicated why they applied for participation in the internet-based treatment was that they found an internet-based intervention easier to integrate into daily life than an regular outpatient therapy (63.5%, n = 127) followed by a general interest in such a new treatment approach (56%, n = 112). Approximately one third (34.5%, n = 69) indicated that they were not willing to use any outpatient face-to-face psychotherapy. Only one fifth (20%, n = 43) of the participants stated that the most important reason for getting involved in the study was that waiting times for psychological therapy were too long. Only the minority of the participants were unsatisfied with former treatment (10.5%, n = 21) or indicated a limited access to treatment (2%, n = 4).

3.2 | Treatment adherence and other treatment

On average, participants in the IG completed 5.18 (SD = 2.65) of the nine sessions (58% of the intervention). Of the 100 individuals participating in the IG, Session 1 was completed by 96 of the participants (96%), Session 2 by 92 (92%), Session 3 by 85 (85%), Session 4 by 71 (71%), Session 5 by 58 (58%), Session 6 by 40 (40%), Session 7 by 31 (31%), Session 8 by 24 (24%), and Session 9 by 21 (21%) of the participants.

In the WLC condition, three participants (3.0%) indicated at T1 that they had received other help within the previous 10 weeks (e.g., psychotherapy and health training other than the StudiCare SAD) as opposed to two participants (2.0%) in the IG condition.

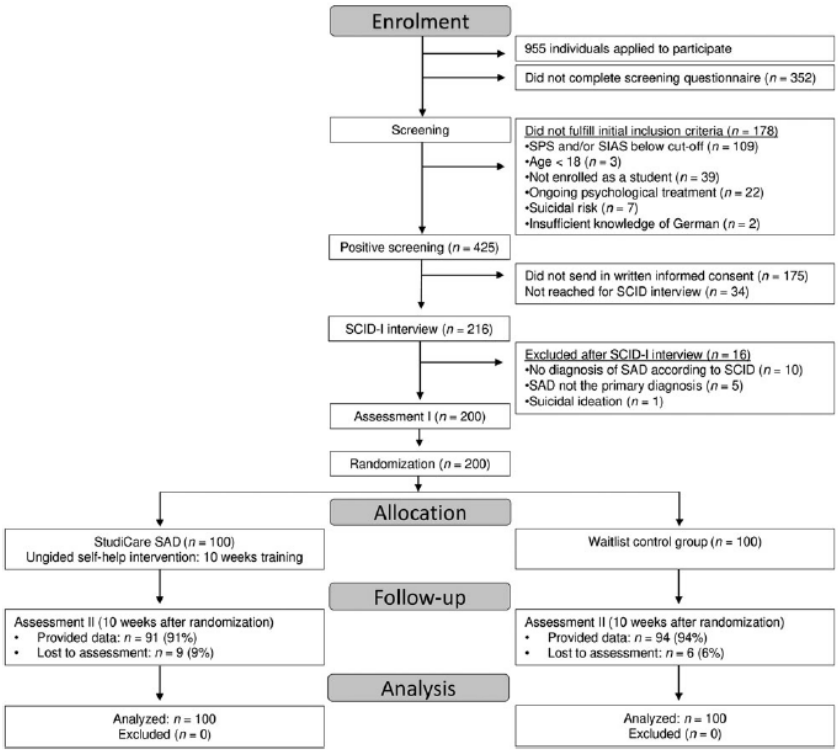


FIGURE 1 Flow of participants. SPS: Social Phobia Scale; SIAS: Social Interaction Anxiety Scale; SAD: social anxiety disorder; SCID-I: Structured Clinical Interview for DSM-IV Axis I Disorders

TABLE 1 Baseline sample characteristics

Characteristic	All participants (*N* = 200)	IG (*n* = 100)	WLC (*n* = 100)
	N (%)	*N* (%)	*N* (%)
Sociodemographic characteristics			
Age (*M*, *SD*)	26.70 (6.34)	26.71 (6.08)	26.68 (6.61)
Gender, female	124 (62.0%)	63 (63.0%)	61 (61.0%)
Married or in a relationship	102 (51.0%)	52 (52.0%)	50 (50.0%)
Citizenship			
Germany	150 (75.0%)	74 (74.0%)	76 (76.0%)
Switzerland	40 (20.0%)	21 (21.0%)	19 (19.0%)
EEA member	3 (1.5%)	1 (1.0%)	2 (2.0%)
No EEA member	7 (3.5%)	4 (4.0%)	3 (3.0%)
Study characteristics			
Full-time student	170 (85.0%)	86 (86.0%)	84 (84.0%)
Part-time student	30 (15.0%)	14 (14.0%)	16 (16.0%)
Semester (*M*, *SD*)	5.09 (3.38)	4.65 (3.15)	5.53 (3.56)
Taking less classes due to SAD	40 (20.0%)	15 (15.0%)	25 (25.0%)
ECTS taken less on average (*M*, *SD*)	2.14 (5.73)	1.49 (4.97)	2.79 (6.36)
Field of study			
Psychology	53 (26.9%)	33 (33.3%)	20 (20.4%)
Medicine & Pharmaceutics	24 (12.2%)	9 (9.1%)	15 (15.3%)
Business & Law	35 (17.8%)	16 (16.2%)	19 (19.4%)
Literature & Media	8 (4.1%)	2 (2.0%)	6 (6.1%)
Educational sciences	13 (6.6%)	4 (4.0%)	9 (9.2%)
Engineering	30 (15.2%)	18 (18.2%)	12 (12.2%)
Linguistics, culture, and social studies	15 (7.6%)	10 (10.1%)	5 (5.1%)
Mathematics and other sciences	19 (9.6%)	7 (7.1%)	12 (12.2%)
Work characteristics			
Employed	106 (53.0%)	58 (58.0%)	48 (48.0%)
Full-time employed	17 (8.5%)	9 (9.0%)	8 (8.0%)
Chronic conditions			
Any chronic condition	127 (64.0%)	66 (66.0%)	61 (61.0%)
Treatment utilization			
Previous psychotherapy	68 (34.0%)	38 (38.0%)	30 (30.0%)
Medication at T0	5 (2.5%)	3 (3.0%)	2 (2.0%)

Note. ECTS: European Credit Transfer System; EEA: European Economic Area; SAD: social anxiety disorder.

3.3 | Primary outcome analyses

3.3.1 | Intervention effect

Changes from baseline to posttest in the IG were large for both primary outcomes according to Cohen's criteria (SPS: d = 1.14, 95% CI [0.84, 1.44]; SIAS: d = 1.17, 95% CI [0.87, 1.47]), whereas within-group changes in the WLC were small to moderate (SPS: d = 0.37, 95% CI [0.09, 0.65]; SIAS: d = 0.32, 95% CI [0.04, 0.6]).

As shown in Table 3, a significant group effect in the ANCOVA indicated lower scores on both primary outcome measures for the IG relatively to the WLC at T1, SPS: $F(1, 197) = 94.65$, $p < 0.001$; SIAS: $F(1, 197) = 122.51$, $p < 0.001$. Effect sizes for differences between the groups were moderate for the SIAS (d = 0.55, 95% CI [0.27, 0.83]) and moderate to large for the SPS (d = 0.76, 95% CI [0.47, 1.04]).

3.3.2 | Treatment response, symptom-free status and symptom deterioration

At T1, more participants in the IG showed reliable improvement compared with those in the WLC based on both the SPS (IG: n = 68, 68%; WLC: n = 32, 32%), $\chi^2(1) = 25.92$, $p < 0.001$, NNT: 2.78, 95% CI [2.04, 4.33], and the SIAS (IG: n = 60, 60%; WLC: n = 24, 24%), $\chi^2(1) = 26.60$, $p < 0.001$, NNT: 2.78, 95% CI [2.05, 4.30].

Compared with WLC, more participants in the IG met the symptom-free criterion at T1 (IG: n = 43, 43%; WLC: n = 19, 19%), $\chi^2(1) = 13.46$, $p = 0.0155$, NNT = 4.17, 95% CI [2.75, 8.61], on both the SPS and the SIAS (IG: n = 24, 24%; WLC: n = 11, 11%), $\chi^2(1) = 5.85$, $p < 0.001$, NNT = 7.70, 95% CI [4.28, 38.12].

At T1, fewer participants in the IG showed reliable deterioration compared with those in the WLC based on both the SPS (IG: n = 12,

TABLE 2 Means and standard deviations for the IG and the WLC groups (ITT sample)

	T0				T1[a]			
	IG		WLC		IG		WLC	
Outcome	*M*	*SD*	*M*	*SD*	*M*	*SD*	*M*	*SD*
Primary outcome								
SPS	34.36	11.79	35.71	13.54	21.03	11.54	30.63	13.72
SIAS	51.47	11.23	48.71	12.92	36.72	13.86	44.36	14.05
Secondary outcome								
BDI-II	12.68	8.23	12.97	7.71	8.12	6.71	11.88	8.16
BSI	0.86	0.49	0.92	0.56	0.56	0.40	0.81	0.57
LSAS	77.61	16.87	76.96	19.57	58.82	20.45	72.51	22.17
IIP-64	1.71	0.39	1.66	0.43	1.34	0.47	1.5	0.48
FPES	43.82	11.00	39.90	13.00	36.17	13.49	39.95	14.6
DPSOS-Self	16.76	4.91	15.85	5.68	14.35	5.42	16.06	5.89
DPSOS-Others	42.51	11.93	40.16	12.56	36.11	14.81	40.60	14.81
AQoL	0.57	0.14	0.58	0.17	0.68	0.16	0.61	0.18
CSQ-8	–	–	–	–	25.15	3.77	–	–

Note. *M*: means; *SD*: standard deviations; IG: intervention group; WTL: waitlist control group; ITT: intention-to-treat; SPS: Social Phobia Scale; SIAS: Social Interaction Anxiety Scale; BDI-II: Beck Depression Inventory II; BSI: Brief Symptom Inventory; LSAS: Liebowitz Social Anxiety Scale; IIP-64: Inventory of Interpersonal Problems; FPES: Fear of Positive Evaluation Scale; DPSOS: Disqualification of Positive Social Outcomes Scale; AQoL: Assessment of Quality of Life; CSQ-8: Client Satisfaction Questionnaire.

[a]Missing data imputed by multiple imputation.

12%; WLC: n = 20, 20%), $\chi^2(1) = 2.38$, $p = 0.12$, and the SIAS (IG: n = 10, 10%; WLC: n = 18, 18%), $\chi^2(1) = 2.66$, $p = 0.10$, although these differences did not reach statistical significance.

3.4 | Secondary outcome analyses

Table 3 shows the results of the ITT analyses for the secondary outcomes, interpersonal problems, depression, somatic symptoms, FPE, and quality of life. The ANCOVAs showed significant between-group effects on all outcomes at the postassessment point, with effect sizes ranging from d = 0.27 (95% CI [0.01, 0.55]) for the FPES to d = 0.64 (95% CI [0.36, 0.92]) for the Liebowitz Social Anxiety Scale.

3.4.1 | Client satisfaction

Client satisfaction with the training was high, as 83% of the participants (n = 70) were "very or mostly satisfied" in general. Most of the

TABLE 3 Results of the ANCOVAs and Cohen's d for the primary and secondary outcome measures (ITT sample) at posttest (T1)

	T1 between-groups effect			T1 within-group effect
	d (95% CI)	ANCOVA[a]		
Outcome		*F*(1, 197)	*p*	
Primary outcome				
SIAS	0.55 [0.83, 0.27]	46.22	<0.001	1.17 [0.87, 1.47]
SPS	0.76 [0.47, 1.04]	40.30	<0.001	1.14 [0.84, 1.44]
Secondary outcome				
BDI-II	0.50 [0.22, 0.78]	16.77	<0.001	0.61 [0.32, 0.89]
BSI	0.49 [0.21, 0.77]	16.66	<0.001	0.66 [0.37, 0.94]
LSAS	0.64 [0.36, 0.92]	15.71	<0.001	1.00 [0.70, 1.29]
IIP-64	0.34 [0.06, 0.61]	16.55	<0.001	0.86 [0.56, 1.14]
FPES	0.27 [0.01, 0.55]	16.66	<0.001	0.62 [0.34, 0.90]
DPSOS-Self	0.30 [0.02, 0.58]	12.56	<0.001	0.47 [0.18, 0.74]
DPSOS-Others	0.30 [0.02, 0.58]	12.58	<0.001	0.48 [0.19, 0.75]
AQoL	0.41 [0.13, 0.69]	19.45	<0.001	0.73 [0.44, 1.01]

Note. ANCOVA: analysis of covariance; ITT: intention-to-treat; SPS: Social Phobia Scale; SIAS: Social Interaction Anxiety Scale; BDI-II: Beck Depression Inventory II; BSI: Brief Symptom Inventory; LSAS: Liebowitz Social Anxiety Scale; IIP-64: Inventory of Interpersonal Problems; FPES: Fear of Positive Evaluation Scale; DPSOS: Disqualification of Positive Social Outcomes Scale; AQoL: Assessment of Quality of Life.

[a]Controlling for pretreatment scores (T0).

participants in the IG group (82%, *n* = 69) rated the quality of the training as being "good" or "excellent." The majority of the participants indicated that the training met "almost all" or "most" of their needs (79%, *n* = 66) and that they have received the kind of training they wanted (80%, *n* = 67; "yes, definitely" or "yes, generally"). Overall, they were satisfied with the amount of training they received (83%, *n* = 70; "very satisfied" or "mostly satisfied"), that the training has helped them "a great deal" or at least "helped" to deal more effectively with their problems (82%, *n* = 69), and that they would use the training again if needed (83%, *n* = 70; "yes, definitely" or "yes, I think so"). In closing, 88% (*n* = 74) of the participants would recommend the IMI to a friend ("yes, definitely" or "yes, I think so").

3.4.2 | Sensitivity analyses

Results of the study completers, including only those participants that provided data, were very similar to those of the ITT analysis, with significant effects on all assessed outcomes and effect sizes at least as large as in the ITT analysis for all outcomes. The between-group effects were smallest for FPES (*d* = 0.25, 95% CI [−0.03, 0.53]) and highest for SPS (*d* = 0.72, 95% CI [0.43, 1.02]).

4 | DISCUSSION

This study evaluated the efficacy of an internet-based unguided self-help intervention for university students with SAD. We found moderate to large effects on social anxiety symptoms for the IG compared with the WLC. The intervention also showed significant effects on all secondary outcome measures including FPE, depression, and quality of life, thus providing evidence for unguided internet-based self-help as an effective format to treat SAD in university students.

The effects found in the present study are in line with the few previous studies targeting SAD symptoms in university students. The only other study on unguided self-help in a sample of students with a confirmed SAD diagnoses and fear of public speaking found significant effects compared with a WLC (Botella et al., 2010). A small pilot study (*N* = 38) on therapist guided self-help found comparable effects for changes in SAD on the SPS (*d* = 1.18 vs. 1.14 in the present study) but somewhat smaller effects with regard to changes on the SIAS (*d* = 0.81 vs. *d* = 1.17 in the present study; Tillfors et al., 2008). Recently, McCall et al. (2018) reported somewhat smaller within-group changes for unguided self-help in a non-clinical student sample with SAD symptoms (SIAS: *d* = 0.72), where between-group effects were comparable with the present study (*d* = 0.56). However, the authors reported completer data only, and the dropout rate in the study was substantial (>35%).

Furthermore, the findings are in concordance with those found for unguided internet-based self-help for SAD in general population samples. The latest meta-analysis on this topic found an average effect of *g* = 0.78 (95% CI [0.50, 1.05]; Kampmann et al., 2016), but with substantial heterogeneity between studies. Effects (*d* = 1.14–1.17, 95% CI [0.84, 1.46]) are also in the range of what is typically found for state-of-the-art face-to-face CBT for SAD (Bandelow et al., 2015; *d* = 1.10, 95% CI [0.93, 1.28]).

Comparing effects on FPE with previous studies is not possible, as we are not aware of any other study that evaluated an intervention that directly targeted FPE. However, Weeks and colleagues reported large pre–post effects for face-to-face CBT that were not specifically targeting FPE. They found a reduction in FPE scores from baseline to posttreatment with a corresponding effect size of *d* = 1.38 (95% CI [1.24, 1.52]) compared with 0.62 (95% CI [0.34, 0.90]) in the present study. As we did not include a comparison condition without a module on FPE, it is not possible to conclude whether the additional FPE module had any incremental effect to the standard treatment, which should be tested in future studies.

Another important finding is that one third (34.5%) of the participants indicated that they would not be willing to utilize traditional available treatment formats such as face-to-face psychotherapy, further highlighting the potential of internet-based treatments for reaching people who were previously not reached by the current health care system (Ebert, Van Daele, et al., 2018a). This finding is in line with studies on barriers of treatment utilization in university students that found attitudinal barriers, such as a preference for self-help or fear of stigma, to be more relevant than structural barriers, such as non-availability, high costs, or long waiting times, in both university students (Ebert, Mortier, et al., 2018) and general population samples (Andrade et al., 2014).

The study has a number of limitations: First, common in randomized trials, there were a small number of cases that did not provide data at follow-up. However, missing data were handled using multiple imputations, and dropout was very low (IG: 9% and CG: 6% after 10 weeks). Therefore, it is unlikely that this has biased the results.

Second, one needs to keep in mind that the evidence provided by the present study is based on a randomized controlled trial (RCT) that is typically characterized by high structuring of participants and a high research attention. As the securing of participants' commitment represents an adherence-promoting element in self-help interventions, it may be the case that the effect sizes are an overestimation of what can be expected when implementing such an intervention into routine care. Hence, a clear concept for ensuring adherence in unguided self-help under routine conditions, such as through minimal guidance, seems favorable (Ebert & Baumeister, 2017).

Third, the elaborated study inclusion process typical for an RCT (i.e., completion of two self-report assessments and sending of informed consent) might have led to the greater inclusion of above-average motivated students, than one could expect outside of the controlled research context. This is a common limitation of RCTs on psychological interventions but may have a particularly high impact on the results of trials on unguided interventions. As a result, the findings might not generalize to unguided self-help without such an inclusion process.

Fourth, although findings clearly indicate that unguided internet-based self-help can result in substantial benefits for students with SAD, it may very well be the case that students are less willing to participate in such a mental health intervention if no support from a health care professional is provided, compared with interventions that include professional guidance. As the effect of any intervention depends on the utilization of the target population, lower overall effects at population level would result, if this should be the case.

Thus, future studies should compare the acceptability of different guidance formats as well as the comparable effects at population level.

Finally, a WLC design with unrestricted access to treatment as usual has been chosen, which may cause some participants in the control condition being less motivated to initiate health-related behavior changes and thus may overaccentuate effects (Ebert & Baumeister, 2017). Finally, follow-up of the results at 6 months will provide information about the sustainability of our internet-based approach.

This study demonstrated that StudiCare SAD is effective in treating SAD when compared with a waitlist control condition. Given the barriers of treatment utilization and high number of untreated university students, it would be worthwhile to integrate such IMIs into routine university health care. Future studies should focus on evaluating effects under routine care conditions.

ACKNOWLEDGEMENTS

The authors gratefully acknowledge the contribution of all participants, research assistants, therapists, and all others who contributed to our study.

FUNDING

This study is cofunded by the BARMER, a German statutory health insurance company. The funders did not have a role in study design, data collection, analysis, interpretation of results, or the decision to publish the study results.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

This study was approved on 13.09.2016 by the Ethics Committee of the Friedrich-Alexander-Universität Erlangen-Nürnberg (ref. no. 260_16 B, 13.09.2016). A written consent was obtained by all participants.

CONSENT FOR PUBLICATION

Not applicable.

AVAILABILITY OF DATA AND MATERIAL

The dataset used in the present study is available from DDE.

DECLARATION OF INTEREST STATEMENT

D. D. E. reports to have received consultancy fees or served in the scientific advisory board from several companies such as Minddistrict, Sanofi, Lantern, Schön Kliniken, German health insurance companies (BARMER and Techniker Krankenkasse), and chambers of psychotherapists. D. D. E. and M. B. are also stakeholders of the Institute for health trainings online (GET.ON), which aims to implement scientific findings related to digital health interventions into routine care. H. B. reports to have received consultancy fees and fees for lectures or workshops from chambers of psychotherapists and training institutes for psychotherapists. In the past 3 years, R. C. K. received support for his epidemiological studies from Sanofi Aventis, was a consultant for Johnson & Johnson Wellness and Prevention, Sage Pharmaceuticals, Shire, and Takeda, and served on an advisory board for the Johnson & Johnson Services, Inc., and Lake Nona Life Project. R. C. K. is a co-owner of DataStat, Inc., a market research firm that carries out health care research.

AUTHORS' CONTRIBUTIONS

D. D. E. and H. B. obtained funding for this study. F. K., D. D. E., T. B., and A. S. have contributed to the study design. F. K. drafted the manuscript, supervised by D. D. E. All authors contributed to the further writing of the manuscript and interpretation of data. All authors read and approved the final manuscript.

ORCID

Fanny Kählke https://orcid.org/0000-0002-8189-301X
Thomas Berger https://orcid.org/0000-0002-2432-7791
Ava Schulz https://orcid.org/0000-0003-2295-9418
Harald Baumeister https://orcid.org/0000-0002-2040-661X
Matthias Berking https://orcid.org/0000-0001-5903-4748
Randy P. Auerbach https://orcid.org/0000-0003-2319-4744
Ronny Bruffaerts https://orcid.org/0000-0002-0330-3694
Pim Cuijpers https://orcid.org/0000-0001-5497-2743
Ronald C. Kessler https://orcid.org/0000-0003-4831-2305
David Daniel Ebert https://orcid.org/0000-0001-6820-0146

REFERENCES

Altman, D. G. (1998). Confidence intervals for the number needed to treat. *BMJ*, *317*(7168), 1309–1312. https://doi.org/10.1136/bmj.317.7168.1309

Andrade, L. H., Alonso, J., Mneimneh, Z., Wells, J. E., Al-Hamzawi, A., Borges, G., … Kessler, R. C. (2014). Barriers to mental health treatment: Results from the WHO World Mental Health surveys. *Psychological Medicine*, *44*(6), 1303–1317. http://doi.org/10.1017/S0033291713001943

Bandelow, B., Reitt, M., Rover, C., Michaelis, S., Gorlich, Y., & Wedekind, D. (2015). Efficacy of treatments for anxiety disorders: A meta-analysis. *International Clinical Psychopharmacology*, *30*(4), 183–192. http://doi.org/10.1097/YIC.0000000000000078

Berger, T., Caspar, F., Richardson, R., Kneubühler, B., Sutter, D., & Andersson, G. (2011). Internet-based treatment of social phobia: A randomized controlled trial comparing unguided with two types of guided self-help. *Behaviour Research and Therapy*, *49*(3), 158–169. http://doi.org/10.1016/j.brat.2010.12.007

Berger, T., Hohl, E., & Caspar, F. (2009). Internet-based treatment for social phobia: A randomized controlled trial. *Journal of Clinical Psychology*, *65*(10), 1021–1035. http://doi.org/10.1002/jclp.20603

Berger, T., Hohl, E., & Caspar, F. (2010). Internetbasierte Therapie der sozialen Phobie: Ergebnisse einer 6-Monate-Katamnese. *Zeitschrift für Klinische Psychologie und Psychotherapie*, *39*(4), 217–221. http://doi.org/10.1026/1616-3443/a000050

Blanco, C., Okuda, M., Wright, C., Hasin, D. S., Grant, B. F., Liu, S.-M., & Olfson, M. (2008). Mental health of college students and their non–college-attending peers. *Archives of General Psychiatry*, *65*(12), 1429. http://doi.org/10.1001/archpsyc.65.12.1429–1437.

Boettcher, J., Berger, T., & Renneberg, B. (2012). Does a pre-treatment diagnostic interview affect the outcome of Internet-based self-help for social anxiety disorder? A randomized controlled trial. *Behavioural and Cognitive Psychotherapy*, *40*(05), 513–528. http://doi.org/10.1017/s1352465812000501

Boß, L., Lehr, D., Reis, D., Vis, C., Riper, H., Berking, M., & Ebert, D. D. (2016). Reliability and validity of assessing user satisfaction with web-

based health interventions. *Journal of Medical Internet Research*, *18*(8), e234. http://doi.org/10.2196/jmir.5952

Botella, C., Gallego, M. J., Garcia-Palacios, A., Guillen, V., Baños, R. M., Quero, S., & Alcañiz, M. (2010). An Internet-based self-help treatment for fear of public speaking: A controlled trial. *Cyberpsychology, Behavior and Social Networking*, *13*(4), 407–421. https://doi.org/10.1089/cyber.2009.0224

Bruffaerts, R., Mortier, P., Kiekens, G., Auerbach, R. P., Cuijpers, P., Demyttenaere, K., … Kessler, R. C. (2018). Mental health problems in college freshmen: Prevalence and academic functioning. *Journal of Affective Disorders*, *225*, 97–103. http://doi.org/10.1016/j.jad.2017.07.044

Chartier, M. J., Hazen, A. L., & Stein, M. B. (1998). Lifetime patterns of social phobia: A retrospective study of the course of social phobia in a nonclinical population. *Depression and Anxiety*, *7*(3), 113–121. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/9656091. https://doi.org/10.1002/(SICI)1520-6394(1998)7:3<113::AID-DA3>3.0.CO;2-C

Clark, D., & Wells, A. (1995). *A cognitive model of social phobia*. New York: Guilford Press.

Cohen, J. (1988). *Statistical power analysis for the behavioral sciences*. Hillsdale, NJ: Lawrence Erlbaum Associates.

Cook, R. J., & Sackett, D. L. (1995). The number needed to treat: A clinically useful measure of treatment effect. *BMJ*, *310*(6977), 452–454. http://doi.org/10.1136/bmj.310.6977.452

Ebert, D. D., & Baumeister, H. (2017). Internet-based self-help interventions for depression in routine care. *JAMA Psychiatry*, *1*(4), 205–215. http://doi.org/10.1001/jamapsychiatry.2017.1394

Ebert, D. D., Buntrock, C., Lehr, D., Smit, F., Riper, H., Baumeister, H., … Berking, M. (2018). Effectiveness of web- and mobile-based treatment of subthreshold depression with adherence-focused guidance: A single-blind randomized controlled trial. *Behavior Therapy*, *49*(1), 71–83. http://doi.org/10.1016/j.beth.2017.05.004

Ebert, D. D., Cuijpers, P., Muñoz, R. F., & Baumeister, H. (2017). Prevention of mental health disorders using internet- and mobile-based interventions: A narrative review and recommendations for future research. *Frontiers in Psychiatry*, *8*. http://doi.org/10.3389/fpsyt.2017.00116

Ebert, D. D., Lehr, D., Heber, E., Riper, H., Cuijpers, P., & Berking, M. (2016). Internet- and mobile-based stress management for employees with adherence-focused guidance: Efficacy and mechanism of change. *Scandinavian Journal of Work, Environment and Health*, *42*(5), 382–394. http://doi.org/10.5271/sjweh.3573

Ebert, D. D., Mortier, P., Kaehlke, F., Bruffaerts, R., Baumeister, H., Auerbach, R. P., … Kessler, R. C. (2018). Barriers of mental health treatment utilization among first year college students: First cross-national results from the WHO World Mental Health International College Student Initiative.

Ebert, D. D., Van Daele, T., Nordgreen, T., Karekla, M., Compare, A., Zarbo, C., … Taylor, J. (2018a). Internet- and mobile-based psychological interventions: Applications, efficacy, and potential for improving mental health. *European Psychologist*, *23*, 167–187. http://doi.org/10.1027/1016-9040/a000318

Ebert, D. D., Van Daele, T., Nordgreen, T., Karekla, M., Compare, A., Zarbo, C., … Taylor, J. (2018b). Internet- and mobile-based psychological interventions: Applications, efficacy, and potential for improving mental health: A report of the EFPA E-Health Taskforce. *European Psychologist*. *Hogrefe Publishing*, *23*, 167–187. http://doi.org/10.1027/1016-9040/a000318

Fergus, T. A., Valentiner, D. P., McGrath, P. B., Stephenson, K., Gier, S., & Jencius, S. (2009). The Fear of Positive Evaluation Scale: Psychometric properties in a clinical sample. *Journal of Anxiety Disorders*, *23*(8), 1177–1183. http://doi.org/10.1016/j.janxdis.2009.07.024

Franke, G. (2000). BSI, Brief Symptom Inventory von L. R. Derogatis (Kurzform der SCL-90-R) - deutsches Manual. *Beltz Test GmbH*.

Furmark, T., Carlbring, P., Hedman, E., Sonnenstein, A., Clevberger, P., Frykman, M., … Andersson, G. (2009). Guided and unguided self-help for social anxiety disorder: Randomised controlled trial. *The British Journal of Psychiatry*, *195*, 440–447. http://doi.org/10.1192/bjp.bp.108.060996.

Gallego, M. J., Emmelkamp, G., Maria, P., van der Kooij, M., & Mees, H. (2011). The effects of a Dutch version of an Internet-based treatment program for fear of public speaking: A controlled study. *International Journal of Clinical and Health Psychology*, *11*(3), 459–472. Retrieved from http://www.redalyc.org/articulo.oa?id=33719289003

Gilbert, P. (2014). Evolutionary models: Practical and conceptual utility for the treatment and study of social anxiety disorder. In *The Wiley blackwell handbook of social anxiety disorder*. Chichester: John Wiley & Sons, Ltd. http://doi.org/10.1002/9781118653920.ch2

Gilles, D. M., Turk, C. L., & Fresco, D. M. (2006). Social anxiety, alcohol expectancies, and self-efficacy as predictors of heavy drinking in college students. *Addictive Behaviors*, *31*(3), 388–398. http://doi.org/10.1016/j.addbeh.2005.05.020

Griffiths, F., Lindenmeyer, A., Powell, J., Lowe, P., & Thorogood, M. (2006). Why are health care interventions delivered over the Internet? A systematic review of the published literature. *Journal of Medical Internet Research*, *8*(2), e10. http://doi.org/10.2196/jmir.8.2.e10

Gültekin, B. K., & Dereboy, F. (2011). The prevalence of social phobia, and its impact on quality of life, academic achievement, and identity formation in university students. Turk Psikiyatri Dergisi. Retrieved from http://www.embase.com/search/results?subaction=viewrecord&from=export&id=L363008230%5Cnhttp://www.turkpsikiyatri.com/PDF/C22S3/en/150-158en.pdf%5Cnhttp://sfx.libis.be/sfxlcl3?sid=EMBASE&issn=13002163&id=doi:&atitle=The+prevalence+of+social+phobia%2C+and+i

Hautzinger, M., Keller, F., & Kühner, C. (2006). *Beck Depressions-Inventar (BDI-II)*. Frankfurt am Main: Harcourt Test Services.

Hedman, E., Andersson, G., Ljótsson, B., Andersson, E., Rück, C., Mörtberg, E., & Lindefors, N. (2011). Internet-based cognitive behavior therapy vs. cognitive behavioral group therapy for social anxiety disorder: A randomized controlled non-inferiority trial. *PLoS One*, *6*(3), e18001. http://doi.org/10.1371/journal.pone.0018001

Heinrichs, N., Hahlweg, K., Fiegenbaum, W., Frank, M., Schroeder, B., & von Witzleben, I. (2002). Validität und Reliabilität der Social Interaction Anxiety Scale (SIAS) und der Social Phobia Scale (SPS). *Verhaltenstherapie*, *12*(1), 26–35. http://doi.org/10.1159/000056690

Horowitz, L., Rosenberg, S. E., Baer, B. A., Ureño, G., & Al, E. (1988). Inventory of interpersonal problems: Psychometric properties and clinical applications. *Journal of Consulting and Clinical Psychology*, *56*(6), 885–892. http://doi.org/10.1037//0022-006x.56.6.885

Horowitz, L., Strauß, B., & Kordy, H. (2000). *Inventar zur Erfassung interpersonaler Probleme: IIP-D; deutsche Version*. Weinheim: Beltz.

Jacobson, N. S., & Truax, P. (1991). Clinical significance: A statistical approach to defining meaningful change in psychotherapy research. *Journal of Consulting and Clinical Psychology*, *59*(1), 12–19. http://doi.org/10.1037//0022-006x.59.1.12

Kählke, F., Berger, T., Schulz, A., Baumeister, H., Berking, M., Cuijpers, P., … Ebert, D. D. (2018). Efficacy and cost-effectiveness of an unguided, internet- and mobile-based self-help intervention for social anxiety disorder in university students: Protocol of a randomized controlled trial. *Manuscript under Review*.

Kampmann, I. L., Emmelkamp, P. M. G., & Morina, N. (2016). Meta-analysis of technology-assisted interventions for social anxiety disorder. *Journal of Anxiety Disorders*, *42*, 71–84. http://doi.org/10.1016/j.janxdis.2016.06.007

Kessler, R. C. (2003). The impairments caused by social phobia in the general population: Implications for intervention. *Acta Psychiatrica Scandinavica*, *108*(s417), 19–27. http://doi.org/10.1034/j.1600-0447.108.s417.2.x

Kessler, R. C., Chiu, W. T., Demler, O., & Walters, E. E. (2005). Prevalence, severity, and comorbidity of 12-month DSM-IV disorders in the National Comorbidity Survey Replication. *Archives of General Psychiatry*, *62*(6), 617. http://doi.org/10.1001/archpsyc.62.6.617–627.

King, S. A., & Poulos, S. T. (1998). Using the Internet to treat generalized social phobia and avoidant personality disorder. *CyberPsychology and Behavior*, *1*(1), 29–36. http://doi.org/10.1089/cpb.1998.1.29

Landis, J. R., & Koch, G. G. (1977). The measurement of observer agreement for categorical data. *Biometrics*, *33*(1), 159. http://doi.org/10.2307/2529310–174.

Liebowitz, M. (1987). Social phobia. *Modern Problems of Pharmacopsychiatry*, *22*, 141–173. https://doi.org/10.1159/000414022

Little, R. J. A., & Rubin, D. B. (2002). *Statistical analysis with missing data*. Hoboken: John Wiley & Sons, Inc. http://doi.org/10.1002/9781119013563

Lopez, G. C., Botella, C., Quero, S., Gomez, A. R., & Baños, R. (2014). Telepsychology program to treat public-speaking anxiety among the Mexican population. *Psicología Iberoamericana*, *22*, 45–55.

Magee, W. J., Eaton, W. W., Wittchen, H.-U., McGonagle, K. A., & Kessler, R. C. (1996). Agoraphobia, simple phobia, and social phobia in the National Comorbidity Survey. *Archives of General Psychiatry*, *53*(2), 159–168. https://doi.org/10.1001/archpsyc.1996.01830020077009

Mattick, R. P., & Clarke, J. C. (1998). Development and validation of measures of social phobia scrutiny fear and social interaction anxiety. *Behaviour Research and Therapy*, *36*(4), 455–470. http://doi.org/10.1016/S0005-7967(97)10031-6

McCall, H. C., Richardson, C. G., Helgadottir, F. D., & Chen, F. S. (2018). Evaluating a web-based social anxiety intervention among university students: Randomized controlled trial. *Journal of Medical Internet Research*, *20*. http://doi.org/10.2196/jmir.8630

Mendlowicz, M. V. (2000). Quality of life in individuals with anxiety disorders. *American Journal of Psychiatry*, *157*(5), 669–682. http://doi.org/10.1176/appi.ajp.157.5.669

Mortier, P., Demyttenaere, K., Auerbach, R. P., Cuijpers, P., Green, J. G., Kiekens, G., … Bruffaerts, R. (2017). First onset of suicidal thoughts and behaviours in college. *Journal of Affective Disorders*, *207*, 291–299. https://doi.org/10.1016/j.jad.2016.09.033

Olfson, M. (2000). Barriers to the treatment of social anxiety. *American Journal of Psychiatry*, *157*(4), 521–527. http://doi.org/10.1176/appi.ajp.157.4.521

Rapee, R. M., & Heimberg, R. G. (1997). A cognitive-behavioral model of anxiety in social phobia. *Behaviour Research and Therapy*, *35*(8), 741–756. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/9256517. https://doi.org/10.1016/S0005-7967(97)00022-3

Richardson, J., Iezzi, A., Khan, M. A., & Maxwell, A. (2014). Validity and reliability of the Assessment of Quality of Life (AQoL)-8D multi-attribute utility instrument. *The Patient - Patient-Centered Outcomes Research*, *7*(1), 85–96. http://doi.org/10.1007/s40271-013-0036-x

Rohde, P., Lewinsohn, P. M., & Seeley, J. R. (1997). Comparability of telephone and face-to-face interviews in assessing axis I and II disorders. *American Journal of Psychiatry*, *154*(11), 1593–1598. http://doi.org/10.1176/ajp.154.11.1593

Runge, A. J., Beesdo, K., Lieb, R., & Wittchen, H.-U. (2008). How frequent is psychotherapy utilisation by adolescents and young adults with anxiety disorders? *Verhaltenstherapie*, *18*(1), 26–34. http://doi.org/10.1159/000113890

Schlarb, A., & Hautzinger, M. (2011). *Klinisch-psychiatrische Ratingskalen für das Kindes-und Jugendalter*. Göttingen: Hogrefe.

Schmidt, J., Lamprecht, F., & Wittmann, W. (1989). Zufriedenheit mit der stationären Versorgung. Entwicklung eines Fragebogens und erste Validitätsuntersuchungen. *Psychotherapie, Psychosomatik,*. Retrieved from http://cat.inist.fr/?aModele=afficheN&cpsidt=7320939

Schulz, A., Stolz, T., Vincent, A., Krieger, T., Andersson, G., & Berger, T. (2016). A sorrow shared is a sorrow halved? A three-arm randomized controlled trial comparing internet-based clinician-guided individual versus group treatment for social anxiety disorder. *Behaviour Research and Therapy*, *84*, 14–26. http://doi.org/10.1016/j.brat.2016.07.001

Schulz, K. F., Altman, D. G., & Moher, D. (2010). CONSORT 2010 statement: Updated guidelines for reporting parallel group randomised trials. *BMJ*, *340*. http://doi.org/10.1136/bmj.c332

Stangier, U., & Heidenreich, T. (2003). Die Liebowitz Soziale Angst-Skala (LSAS). In Collegium Internationale Psychiatriae Scalarum (Ed.), *Internationale Skalen für Psychiatrie*. Göttingen: Hogrefe.

Stangier, U., Heidenreich, T., Berardi, A., Golbs, U., & Hoyer, J. (1999). Die Erfassung sozialer Phobie durch die Social Interaction Anxiety Scale (SIAS) und die Social Phobia Scale (SPS). *Zeitschrift F {ü} r Klinische Psychologie Und Psychotherapie*, *28*(1), 28–36. http://doi.org/10.1026//0084-5345.28.1.28

Stangier, U., Heidenreich, T., & Peitz, M. (2009). *Soziale Phobien: ein kognitiv-verhaltenstherapeutisches Behandlungsmanual; mit CD-ROM*. Weinheim: Beltz.

Stolz, T., Schulz, A., Krieger, T., Vincent, A., Urech, A., Moser, C., … Berger, T. (2018). A mobile app for social anxiety disorder: A three-arm randomized controlled trial comparing mobile and PC-based guided self-help interventions. *Journal of Consulting and Clinical Psychology*, *86*(6), 493–504. http://doi.org/10.1037/ccp0000301

Tillfors, M., Carlbring, P., Furmark, T., Lewenhaupt, S., Spak, M., Eriksson, A., … Andersson, G. (2008). Treating university students with social phobia and public speaking fears: Internet delivered self-help with or without live group exposure sessions. *Depression and Anxiety*, *25*(8), 708–717. http://doi.org/10.1002/da.20416

Tillfors, M., & Furmark, T. (2007). Social phobia in Swedish university students: Prevalence, subgroups and avoidant behavior. *Social Psychiatry and Psychiatric Epidemiology*, *42*(1), 79–86. http://doi.org/10.1007/s00127-006-0143-2

Titov, N., Andrews, G., Choi, I., Schwencke, G., & Johnston, L. (2009). Randomized controlled trial of web-based treatment of social phobia without clinician guidance. *Australian & New Zealand Journal of Psychiatry*, *43*(10), 913–919. http://doi.org/10.1080/00048670903179160

Titov, N., Andrews, G., Choi, I., Schwencke, G., & Mahoney, A. (2008). Shyness 3: Randomized controlled trial of guided versus unguided Internet-based CBT for social phobia. *The Australian and New Zealand Journal of Psychiatry*, *42*(12), 1030–1040. http://doi.org/10.1080/00048670802512107

Titov, N., Andrews, G., Schwencke, G., Robinson, E., Peters, L., & Spence, J. (2010). Randomized controlled trial of Internet cognitive behavioural treatment for social phobia with and without motivational enhancement strategies. *The Australian and New Zealand Journal of Psychiatry*, *44*(10), 938–945. http://doi.org/10.3109/00048674.2010.493859

Wang, P. S., Berglund, P., Olfson, M., Pincus, H. A., Wells, K. B., & Kessler, R. C. (2005). Failure and delay in initial treatment contact after first onset of mental disorders in the National Comorbidity Survey Replication. *Archives of General Psychiatry*, *62*(6), 603. http://doi.org/10.1001/archpsyc.62.6.603–613.

Weeks, J. W. (2010). The Disqualification of Positive Social Outcomes Scale: A novel assessment of a long-recognized cognitive tendency in social anxiety disorder. *Journal of Anxiety Disorders*, *24*(8), 856–865. http://doi.org/10.1016/j.janxdis.2010.06.008

Weeks, J. W., Heimberg, R. G., & Rodebaugh, T. L. (2008). The Fear of Positive Evaluation Scale: Assessing a proposed cognitive component of social anxiety. *Journal of Anxiety Disorders*, *22*(1), 44–55. http://doi.org/10.1016/j.janxdis.2007.08.002

Weeks, J. W., Heimberg, R. G., Rodebaugh, T. L., Goldin, P. R., & Gross, J. J. (2012). Psychometric evaluation of the Fear of Positive Evaluation Scale in patients with social anxiety disorder. *Psychological Assessment*, *24*(2), 301–312. http://doi.org/10.1037/a0025723

Weeks, J. W., Heimberg, R. G., Rodebaugh, T. L., & Norton, P. J. (2008). Exploring the relationship between fear of positive evaluation and social anxiety. *Journal of Anxiety Disorders*, *22*(3), 386–400. http://doi.org/10.1016/j.janxdis.2007.04.009

Weeks, J. W., & Howell, A. N. (2012). The bivalent fear of evaluation model of social anxiety: Further integrating findings on fears of positive and

negative evaluation. *Cognitive Behaviour Therapy*, *41*(2), 83–95. http://doi.org/10.1080/16506073.2012.661452

Weeks, J. W., & Howell, A. N. (2014). Fear of positive evaluation: The neglected fear domain in social anxiety. In *The Wiley Blackwell handbook of social anxiety disorder*. John Wiley & Sons, Ltd. http://doi.org/10.1002/9781118653920.ch20

Weeks, J. W., Jakatdar, T. A., & Heimberg, R. G. (2010). Comparing and contrasting fears of positive and negative evaluation as facets of social anxiety. *Journal of Social and Clinical Psychology*, *29*(1), 68–94. http://doi.org/10.1521/jscp.2010.29.1.68

Werner, K. H., Goldin, P. R., Ball, T. M., Heimberg, R. G., & Gross, J. J. (2011). Assessing emotion regulation in social anxiety disorder: The emotion regulation interview. *Journal of Psychopathology and Behavioral Assessment*, *33*(3), 346–354. http://doi.org/10.1007/s10862-011-9225-x

Wittchen, H.-U., & Jacobi, F. (2005). Size and burden of mental disorders in Europe—A critical review and appraisal of 27 studies. *European Neuropsychopharmacology*, *15*(4), 357–376. http://doi.org/10.1016/j.euroneuro.2005.04.012

Wittchen, H.-U., Jacobi, F., Rehm, J., & Gustavsson, A. (2011). The size and burden of mental disorders and other disorders of the brain in Europe 2010. *European Neuropsychopharmacology*, *21*, 655–679. https://doi.org/10.1016/j.euroneuro.2011.07.018.

Zarski, A.-C., Lehr, D., Berking, M., Riper, H., Cuijpers, P., & Ebert, D. D. (2016). Adherence to internet-based mobile-supported stress management: A pooled analysis of individual participant data from three randomized controlled trials. *Journal of Medical Internet Research*, *18*(6), e146, 1–15. http://doi.org/10.2196/jmir.4493

How to cite this article: Kählke F, Berger T, Schulz A, et al. Efficacy of an unguided internet-based self-help intervention for social anxiety disorder in university students: A randomized controlled trial. *Int J Methods Psychiatr Res*. 2019;e1766. https://doi.org/10.1002/mpr.1766

3.3. Article 3: Long-term efficacy and cost-effectiveness of an IMI for SAD

Authors: Fanny Kählke, Claudia Buntrock, Filip Smit, Thomas Berger, Harald Baumeister & David D. Ebert

Title: Long-term Outcomes and Cost-Effectiveness of an Internet- and Mobile-Based Self-Help Intervention for Social Anxiety Disorder in University Students: A Randomized Controlled Trial

Journal: Manuscripts submitted to the *Nature Human Behaviour* (currently under review, 2022)

Trial register: https://www.drks.de/ DRKS00011424

Social anxiety disorder (SAD) is widespread among university students. SAD is associated with adverse consequences reaching from low quality of life over increased alcohol consumption to productivity losses. The resulting healthcare expenditures generate high costs for society. Internet- and mobile-based interventions (IMIs) can overcome treatment barriers and are effective in the short-term. Yet, evidence for their long-term effects and cost-effectiveness is scarce. This randomized-controlled trial examined the efficacy and cost-effectiveness of an unguided IMI for university students with SAD 6 months after randomization. Students diagnosed with SAD (N = 200) were randomly assigned to an IMI or a waitlist control condition (WLC) with unrestricted access to treatment as usual. The IMI consists of 9 sessions based on the cognitive-behavioral approach by Clark and Wells. The primary outcome was SAD symptom severity assessed via the Social Phobia Scale (SPS) and the Social Interaction Anxiety Scale (SIAS). A health economic evaluation investigated the generated costs related to symptom-free status and quality-adjusted life years (QALYs based on the AQoL-8D instrument), each from a societal and healthcare perspective. Costs were assessed by the Trimbos Institute and Institute of Medical Technology Questionnaire for Costs Associated with Psychiatric Illness (TiC-P) adapted to the German healthcare system. Intervention costs were €178.5 including maintenance, hosting, and 19% value added tax. Effects found at post-treatment favoring the IMI were maintained at 6-month follow-up [SIAS (Cohen's *d* = 0.59; 95% confidence interval, CI [0.30, 0.87]), SPS (*d* = 0.83; 95% CI [0.54, 1.1]). From a societal perspective, the intervention generated higher effects at lower costs compared with WLC showing a 92% and 93% (willingness to pay [WTP] = 0) probability of cost-effectiveness related to both a symptom-free status and per QALY gained. From a healthcare perspective, the IMI led to higher effects at higher cost compared to WLC, thus the likelihood of the intervention's cost-effectiveness was 97% per symptom-free status (WTP = €1,000) and 96% per QALY gained (WTP = €6,000). This IMI was efficacious and cost-effective being under the cost-effectiveness threshold of £30,000 per QALY gained compared to WLC

from a societal and healthcare perspective. Decision makers and clinicians can easily use this scalable treatment that addresses known treatment barriers in SAD patients.

The manuscript was submitted in October 2022 to *Nature Human Behaviour*. This online open-access journal is dedicated to publishing high quality peer-reviewed research in all aspects of human behavior from across social and natural sciences.

Contribution: Fanny Kählke was the principal investigator and author of the published article. David D. Ebert and Harald Baumeister obtained funding for this study as part of the StudiCare project. Thomas Berger developed the evaluated intervention. Fanny Kählke, supported by David D. Ebert, Thomas Berger, and Ava Schulz, developed the conception of the study design. Fanny Kählke conducted the study, prepared, and analyzed the dataset. She wrote the published article and was supervised by Claudia Buntrock and David D. Ebert. All co-authors read, critically revised, and finally approved the published article.

Corresponding author

Fanny Kählke, M. Ed. M.Sc.
Email: fanny.kaehlke@tum.de

Long-term Outcomes and Cost-Effectiveness of an Internet-Based Self-Help Intervention for Social Anxiety Disorder in University Students: A Randomized Controlled Trial

Fanny Kählke[*1], Claudia Buntrock[2], Filip Smit[3,4,5], Thomas Berger[6], Harald Baumeister[7], David Daniel Ebert[1]

[1] Faculty of Sport and Health Sciences, Professorship for Psychology and Digital Mental Health Care, Technical University of Munich, Munich, Germany

[2] Institute for Social Medicine and Health Systems Research, Otto-von-Guericke-Universität Magdeburg, Magdeburg, Germany

[3] Department of Clinical, Neuro and Developmental Psychology, Amsterdam Public Health research institute, Vrije Universiteit, Amsterdam, Netherlands

[4] Department of Epidemiology and Biostatistics, Amsterdam Public Health research institute, VU University Medical Center, Amsterdam, Netherlands

[5] Center of Health Economic Evaluation, Trimbos Institute (Netherlands Institute of Public Mental Health), Utrecht, Netherlands

[6] Department of Clinical Psychology and Psychotherapy, Universität Bern, Bern
Switzerland

[7] Department of Clinical Psychology and Psychotherapy, Ulm University, Ulm, Germany

Trial registration:
German Clinical Trials Register (DRKS):
DRKS00011424

Social anxiety disorder (SAD) is widespread among university students and associated with high costs for the society. While unguided internet- and mobile-based interventions (IMIs) may have short-term effects in reducing SAD symptoms, evidence for their long-term efficacy and cost-effectiveness is still limited. The aim of this study is to examine the 6-month outcomes of an IMI for university students with SAD. Students diagnosed with SAD (N = 200) were randomly assigned to an IMI or a waitlist control (WLC) condition. The IMI consisted of nine sessions based on the cognitive-behavioral treatment model for social phobia by Clark and Wells. The primary outcome was SAD symptom severity assessed via the Social Phobia Scale (SPS) and the Social Interaction Anxiety Scale (SIAS). A health economic evaluation from a societal and healthcare perspective examined both the costs related to symptom-free status and quality-adjusted life years (QALYs) gained. Statistically significant differences in SAD symptom severity were found at post-treatment favoring the IMI and maintained at a 6-month follow-up [SPS (Cohen's d = 0.83; 95% CI, 0.54, 1.1), SIAS (Cohen's d = 0.59; 95% CI, 0.30, 0.87)]. From the societal perspective, at a willingness to pay (WTP) of €0, the intervention was found to have a 92% and a 93% probability of cost-effectiveness compared with WLC per symptom-free status and QALY gained, respectively. In a healthcare perspective, the intervention's probability of being cost-effective was 97% per symptom-free status at a WTP of €1,000 (US$1,326) and 96% per QALY gained at a WTP of €6,000 (US$7956). This IMI was effective in treating university students with SAD and had an acceptable likelihood of cost-effectiveness compared with WLC from the societal perspective. It may also attract the attention of decision makers and clinicians as it is scalable, shows a high probability of being cost-effective, and overcomes known treatment barriers in SAD patients.

Keywords: social anxiety disorder, internet-based intervention, unguided self-help, university students, cost-effectiveness, cost-utility, economic evaluation

Introduction

Social anxiety disorder (SAD) is a prevalent and impairing disorder and is considered a public health concern. Especially students fall within the age range when common mental health problems reach their developmental peak. Being at a university is associated with many stressors and transitional events.[1] In Germany, persons aged 18–35 show a 4.8%[2] 12-month prevalence of SAD, while 12.2% of university students show clinically relevant social phobic symptoms.[3] Several adverse effects on quality of life (QoL) and identity formation,[4] alcohol consumption[5], and suicidal ideation[6] are reported in university students with SAD. These may lead to premature dropout and academic underachievement.[7] Moreover, SAD is associated with substantial impairment across several domains, such as relationship, daily and social life, and work.[8] Altogether, it generates direct (treatment), indirect (productivity losses, absence of work, low qualification[9,10]), and intangible costs (lower QoL, social impairment). In Germany, the mean total 6-month costs for SAD in a clinical sample were estimated at €4,802 per person, which are mainly attributed to indirect cost.[11]

While the university setting enables comprehensive approaches for prevention, early intervention, and treatment of students with SAD, students in general are averse to conventional student counseling centers.[12] In particular, students with SAD face attitudinal barriers (fear of stigmatization and negative evaluation) to help-seeking[13] that may leave them untreated with a chronic condition.[14] Internet- and mobile-based interventions (IMIs), which are flexible, accessible, and anonymous,[15–17] present a promising approach to reach those affected individuals. Unguided IMIs have received adequate attention owing to their potential for high scalability and relatively low marginal costs. The efficacy of unguided IMIs based on cognitive-behavioral approaches targeting SAD has been shown with medium effects at post-treatment compared with passive controls (g = 0.78, 95% CI [0.50–1.05], SE = 0.14, $p < 0.001$, k = 5). However, in contrast to guided IMIs, the evidence for the long-term efficacy of unguided IMIs is still limited.[18–21]

Moreover, the value of IMIs for SAD in university students has not been sufficiently investigated. Existing evidence suggests that IMIs targeting SAD in university students might have beneficial effects up to one year with or without guidance.[22–24] However, the evidence base is weak because studies mainly focused on fear of public speaking,[22,24] had substantial dropout rate,[23,24] and were underpowered.[22]

Apart from the efficacy of IMIs for SAD, evidence to support their cost-effectiveness is still insufficient. While the assessment of the efficacy takes the benefits for patients into account, the assessment of economic consequences also considers a wider perspective by providing insights into societal costs and benefits. Merely three studies investigated the economic merits of IMIs for SAD, indicating that guided[25–27] and unguided[28] IMIs may be a cost-effective treatment option in the long-term (≥ 6 months) in the general population. However, it should be considered that evidence is still limited due to high dropout rates[28], limited statistical analyses, and the absence of a full health economic evaluation.[27]

Previously published results of this study (10 weeks after randomization) showed that IMI was superior to a waitlist control (WLC) group in reducing SAD symptom severity in university students with moderate to large effect sizes.[29] In this study, we report its clinical effects at 6-month follow-up and the health economic outcomes from a societal and public healthcare perspective over a 6-month period.

Methods

Study design and participants

A two-arm randomized controlled design was used to allocate 200 participants (block size of 8, varying ratio) to either the intervention (IMI) or control (WLC) group. Alongside this trial, a cost-effectiveness analysis was conducted. An independent researcher, not otherwise involved in the study, performed the randomization using the program Randlist.[31] Self-reported measurements were collected over three measurement points using a secured web-based assessment system (UNIPARK,[32] 256-bit encrypted): at baseline (T0), post-treatment (T1; 10 weeks after randomization), and 6-month follow-up (T2). The participants were recruited via e-mails sent to enrolled students at universities in Switzerland (N = 3), Austria (N = 2), and Germany (N = 8) from January 2017 to February 2018. The applicants were included in the study if they were 18 years or older, scored >21 on the Social Phobia Scale (SPS) and/or > 32 on the Social Interaction Anxiety Scale (SIAS), met the diagnostic criteria of SAD according to the structured clinical interview for DSM-IV axis I disorders (SCID-I) and provided written informed consent. The interviews were conducted by trained interviewers via telephone.[33] The exclusion criteria included individuals at risk of suicide, showing dissociative symptoms, being diagnosed with a psychosis, or currently undergoing psychotherapy. The Ethics Committee of the Friedrich-Alexander-University Erlangen Nuremberg, Germany, approved the study. The trial was registered in the

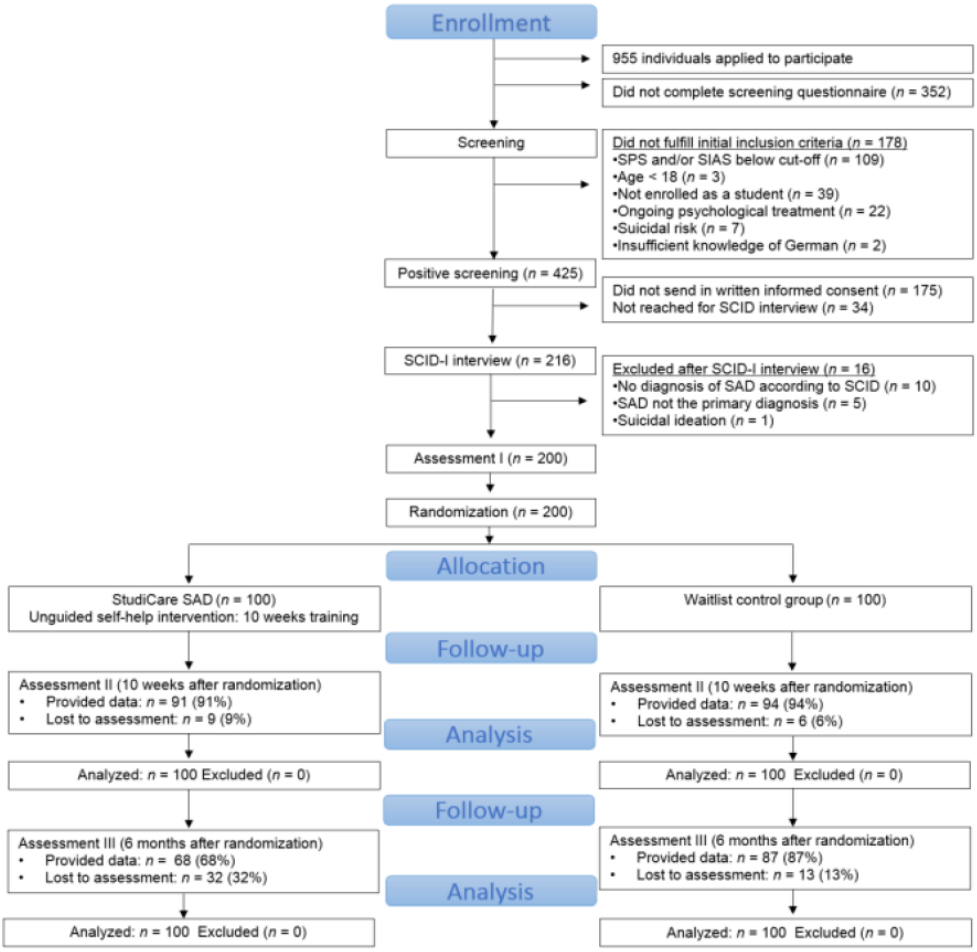


Figure 1 Flow of participants

German clinical trial registry (DRKS00011424) on December 14th, 2016. More details on the study design and participants can be found in the study protocol.[30]

Intervention

The intervention consisted of nine weekly sessions (approx. 60 minutes) based on the cognitive-behavioral treatment of Clark and Wells (1995).[34,35] It contained text-based information material, various exercises (e.g., attention training), and diaries (e.g., identifying and questioning negative thoughts). The sessions were based on motivational enhancement (Session 1), psychoeducation (Session 2), identification and modification of negative thoughts through a thought diary (Sessions 3) and cognitions related to fear of positive evaluation (FPE) (Session 4), exercises to reduce self-focused attention, including behavioral experiments, such as in vivo exposures (Sessions 5–7), healthy lifestyle and problem-solving skills (Session 8), and relapse prevention (Session 9). The focus on FPE reflected a new treatment element that included the core components of SAD: fear of negative and positive evaluation.[36] A detailed description of the intervention can be found elsewhere.[30]

Outcome Measures

Primary outcome

The level of social anxiety was measured by the SPS and the SIAS.[37] These two self-report questionnaires complement each another and are usually administered together. The SIAS assesses more general fears of social interaction, whereas the SPS focuses on fears of being judged by others during daily activities. Each scale consists of 20 items rated on a 5-point Likert scale (0 = "not at all" to 4 = "extremely"). These two scales have found to be valid, reliable, and useful for clinical and research purposes.[38] Cronbach's α for the SIAS and SPS ranged from 0.90 to 0.94[39] [current sample, α = 0.91–0.93]. Symptom-free status was operationalized as scoring ≤17 on the SPS and ≤ 26 on the SIAS.[40] Stangier et al.[37] proposed these cut-off values to differentiate between social phobic cases and non-social phobic cases. Diagnostic

status was assessed via a diagnostic interview (SCID-I) by an interviewer blinded to the treatment condition after 6 months. Interrater reliability was evaluated in 20% of randomly selected participants.

Secondary outcomes

The secondary outcomes are as follows:

- Symptoms of social anxiety (the Liebowitz Social Anxiety Scale [LSAS-SR] assesses fear and avoidance in 24 different situations)[41] (Cronbach's α = 0.95 in the current sample)
- Fear of positive evaluation (Fear of Positive Evaluation Scale [FPES] showing good psychometric properties in clinical and healthy samples [10 items][42,43] [α = 0.79], Disqualification of Positive Social Outcomes Scale [DPSOS] [13 items][44] [α = 0.90])
- Depressive symptoms (Beck Depression Inventory II [BDI-II] [21 items] has shown high reliability and validity in SAD clients)[35,45] (α = 0.91)
- General psychopathology (Brief Symptom Inventory [BSI] [53 items, 9 dimensions], Global Severity Index [GSI] as overall mean score reported and robust psychometric properties)[46,47] (α = 0.96)
- Interpersonal problems (Inventory of Interpersonal Problems [IIP-64] [8 dimensions] has shown adequate psychometric properties)[48,49] (α = 0.96)

Health economic evaluation

Quality-adjusted life years (QALYs)

QALYs were computed using the Assessment of Quality of Life (AQol-8D) and the EuroQol (EQ-5D-5L) instruments. The AQol-8D assesses eight dimensions (independent living, pain, senses, mental health, happiness, coping, relationships, self-worth) and is a reliable and valid instrument[50] with a Cronbach's α of 0.96. The EQ-5D-5L is a widely applied, valid, and reliable measurement of QoL.[51] It consists of five items on a 5-point Likert scale related to mobility, self-care, common activities, pain/discomfort, and anxiety/depression. Utility values were derived using instrument-specific utility weights (EQ-5D,[52] AQol[53]). QALYs were calculated using the area under the curve (AUC) method of linearly interpolated utilities between measurements to cover the whole 6-month follow-up period. The EQ-5D was only used for sensitivity analyses.

Costs

We retrospectively assessed the 3-month healthcare costs, productivity losses, and patient and family costs using the "Trimbos Institute and Institute of Medical Technology Questionnaire for Costs Associated with Psychiatric Illness" (TiC-P) adapted to the German healthcare system.[54] The TiC-P is a widely used and reliable instrument for collecting self-reported data on healthcare utilization and productivity losses in patients with mental health conditions.[55] The German version has been used in a number of RCTs.[56,57] Standard unit cost prices were multiplied by the units of resource use for each participant[58] The current market price of the intervention was estimated at €150 (US$ 198.89) per participant, reflecting costs due to maintenance and hosting. In addition to the German value added tax of 19%, the interventions costs were €178.50 (US$ 236.68). It was assumed that every participant owned a computer and had access to the internet. The costs of therapeutic appliances and medication were obtained from the Lauer-Taxe[59] and calculated according to the method of Bock et al.[58] German healthcare costs were last published in 2011 and therefore, indexed from 2011 to 2017 (index factor of 1.09) based on the German consumer price index.[60]

Costs stemming from productivity losses through absenteeism and presenteeism were only assessed in students who had a paid job. Absenteeism costs were calculated applying the human capital approach.[61] Thus, the number of lost work days was multiplied by the student's average gross daily wage based on their reported monthly salary. Students also reported the number of workdays which were less efficient. These days were multiplied by an inefficiency score (the Osterhaus method[62]), which resulted in lost work day equivalents due to presenteeism. Subsequently, their gross wages per day were used to calculate the costs that occurred due to presenteeism. Productivity losses generated by unpaid work, such as daily chores, were valued using a shadow price of €19.63 (US$ 26.03) per hour for domestic help. Table S1 shows additional costing information.

Cumulated costs were estimated using the AUC method to linearly interpolate the costs over the period of three months, which are measured at each measurement point to cover the full follow-up period of 6 months.[63] All costs were calculated in Euros (€) for 2017 (December), the year in which the study was conducted. Costs were converted to US dollars[64] using the purchasing power parities reported by the Organization for Economic Cooperation and Development for the reference year 2017; €1 was equated to US$1.33. The resource utilization in Austria and Switzerland was valued using German standard unit cost prices to increase consistency in costs and minimize confounding.

Evaluation of clinical outcomes

This study was conducted to detect a mean standardized difference of d = 0.40 in the primary outcomes (SPS/ SIAS) between the groups at post-measurement.[65] The results were reported according to the Consolidated Standards

of Reporting Trials statement using intention-to-treat (ITT) procedures.[66] Missing clinical outcome data were imputed by applying a Markov Chain Monte Carlo multivariate imputation algorithm with 10 estimations per missing value.[67]

The evaluation of the clinical outcomes was performed using the SPSS software.[68] The IMI and WLC were compared six months after randomization (T2) using analysis of covariance (ANCOVA) with baseline levels as covariates. Due to the violation of normally distributed error terms of many outcomes, robust ANCOVA was used.[69] These analyses were adjusted for multiple testing. Hence, α was set at a level of <0.025[70] for testing the primary outcomes and <0.05 for all other tests. Cohen's *d* with 95% CIs was calculated.

Treatment response and clinically significant deterioration were defined by the Reliable Change Index as proposed by Jacobson and Truax.[37] The participants were defined as reliably improved if their SPS (SIAS) score declined from baseline to 6-month follow-up with more than 1.96 standard units, while also considering the reliability of the measurement instruments to compensate for random measurement error. The participants met the criteria for reliable change when they had improved (deteriorated) at least 7.03 points on the SPS and 9.53 points on the SIAS, respectively. Moreover, the participants were rated as symptom-free if they scored 17 or below on the SPS and 26 or below on the SIAS.[37] To further guide the clinical interpretation, the numbers needed to treat (NNT) were calculated.[71,72] Differences in symptom-free status, reliable change, and diagnostic status as assessed by SCID interviews between the groups were assessed at follow-up using the chi-squared test.

Health economic evaluation

The evaluation followed the guidelines from the International Society For Pharmacoeconomics and Outcomes Research (ISPOR RCT-CEA Task Force Report) and the recommendations of the Consolidated Health Economic Evaluation Reporting Standard (CHEERS).[73,74]

All data was analyzed based on the ITT principle. Thus, missing cost data was imputed using the regression imputation procedure using the predictors of the outcome (e.g., baseline costs, annual gross salary, status of employment) and dropout rate (e.g., sex, age) that were identified via logistic regression analysis.

Adjusted QALYs were estimated using ordinary least squares (OLS) regression controlled for baseline utility values. From a societal and public healthcare perspective, cost categories and costs per study group were assessed by OLS regression models. One cost outlier was identified by calculating the Mahalanobis distance based on the total cost (N = 1, in the WLC) and handled using winsorization where cost outliers are not removed but their extreme values are replaced by the value at the 99th percentile.[75] No discounting of costs and effects was applied because the follow-up period did not exceed one year. The incremental cost-effectiveness ratio (ICER) was calculated as incremental costs per unit of the effect (QALY, symptom-free status). The ICER was calculated as ICER = ($costs_{IMI}$–$costs_{WLC}$) / ($effects_{IMI}$–$effects_{WLC}$), where the costs are cumulated *Costs* over the 6-month period and *Effects* are QALY gains or symptom-free status.

A probabilistic decision-making approach for our economic analyses was adopted, which[76] takes the stochastic uncertainty of the trial data into account[77] and informs the decision makers on probabilities rather than on statistical significance. The incremental costs and effects were obtained from a 5000-fold bootstrapped seemingly unrelated regression equation model on costs and effects, while adjusting for baseline utilities, age, and prior psychotherapy.[78] The 5000 bootstrap replications of costs and effect pairs were used to obtain 95% confidence intervals and to be plotted in a cost-effectiveness plane. The plane depicts the incremental effects between the intervention and control group on the x-axis and the incremental costs between the groups on the y-axis. The intervention "dominates" the control groups if better effects are obtained for lower costs. Hence, the majority of simulated ICER fall in the southeast quadrant. In contrast, in the northwest quadrant, the intervention is "inferior" to the control group as higher costs are associated with worse health outcomes. Thus, it is not considered cost-effective.[61] In the southwest quadrant, an intervention is less effective and less costly than the control group. On the other hand, in the northeast quadrant, an intervention is more effective and more costly than the control condition. Here the amount of money a decision maker is willing to pay for one additional positive outcome determines the adoption of a new intervention. Since the WTP ceiling for gaining one unit of health (e.g., gaining one QALY) is an unknown quantity, a cost-effectiveness acceptability curve was presented, which displays the probability of cost-effectiveness of IMI at varying WTP ceilings. All analyses were performed using Stata version 16.1.[79]

Sensitivity analyses

The sensitivity analyses were conducted to inspect the robustness of our results. First, the data of the participants who completed the 6-month follow-up assessment were analyzed. Second, changing market prices can lead to varying intervention costs, which explains why the increased intervention costs were examined (+50%, 100%). Third, Swiss students (n = 40, 20%) were excluded to validate the robustness of the findings. Their number and employment rate were balanced across groups, but differences in healthcare settings and salaries could have biased the results. Fourth, to facilitate comparability across studies, the widely applied EQ-5D instrument was used to generate QALYs. Lastly, the diagnostic status as a meaningful

effect outcome for policymakers was used for cost-effectiveness analysis.

Results

Sample

The sample predominately consisted of female (n = 124, 62%) German university students (n = 150, 75%) aged 27 (SD 6.34) (Table S2). A comprehensive description of the study sample and the participant flow can be found elsewhere.[30] We did not observe any clinically relevant baseline differences between the study conditions. The attrition rate was 22.5% (45/200) at the 6-month follow-up. The dropout rates between IMI (n = 32/100, 32%) and WLC (n = 13/100, 13%) differed significantly (χ^2 = 10.35; df = 1; p < 0.01) yet the dropout rate was not associated with the sociodemographic factors nor the baseline SAD symptoms.

Outcome measures

As shown in Table 1, IMI was associated with lower scores on both primary outcome measures than WLC. These between-group differences were statistically significant: SPS, F (1, 197) = 55.01, p < 0.001; SIAS, F (1, 197) = 49.03, p < 0.001. The corresponding standardized effect sizes were moderate for SIAS (d = 0.59, 95% CI [0.30, 0.87]) and large for SPS (d = 0.83, 95% CI [0.54, 1.10]). Fewer participants in the IMI (n = 30/100) than in the WLC (n = 60/100) presented with a clinical diagnosis of social phobia assessed through a SCID interview (χ^2 = 18.18; df = 1; p < 0.001). The interrater reliability showed substantial agreement (Cohen's Kappa, κ = 0.78[80]).

Treatment response, symptom-free status, and symptom deterioration

After 6 months, significantly more participants in the IMI showed a reliable improvement and achieved a symptom-free status compared with those in the WLC based on the SPS and the SIAS. Likewise, the clinically significant deterioration was lower in the IMI compared with the WLC for both outcomes (Table S3).

Secondary outcome analyses

Table 2 shows the results for the secondary outcomes, interpersonal problems, depression, somatic symptoms, FPE, and QoL. Significant between-group differences for all outcomes, except the EQ-5D, with effect sizes ranging from d = 0.23 (95% CI [0.05, 0.50]) for the AQoL to d = 0.76 (95% CI [0.47, 1.05]) for the LSAS-SR were observed.

Health Economic Evaluation

Health outcomes

Regarding symptom-free status, the IMI significantly differed from WLC on the SPS (incremental effect (Δ[E] = 0.26, CI 95% 0.15–0.37)) and on the SIAS (incremental effect (Δ[E] = 0.24; 95% CI, 0.14–0.34)), respectively. On average, the participants in the IMI gained 0.66 QALYs (95% CI, 0.64–0.67) during follow-up, whereas the participants in the WLC gained 0.61 QALYs (95% CI, 0.59–0.62). Statistically significant differences in the adjusted incremental QALYs were observed (Δ[E] = 0.046; 95% CI, 0.02–0.07).

Costs

At baseline, the mean total costs only differed (€138; US$ 183) moderately between the IMI (€464, US$615) and the WLC (€603; US$800). Table 3 shows the average 6-month accumulated costs per participant by study condition. After 6 months, the total incremental costs were €-211 in favor of the intervention group (IMI, €850; WLC, €1061). The average healthcare costs were €106 or higher in the IMI (€345) compared with WLC (€240). The patient and family costs were similar in both groups slightly favoring the IMI. Productivity losses especially presenteeism at work produced the highest cost differences of €-227 (IMI, €391; WLC, €618) exceeding the intervention costs.

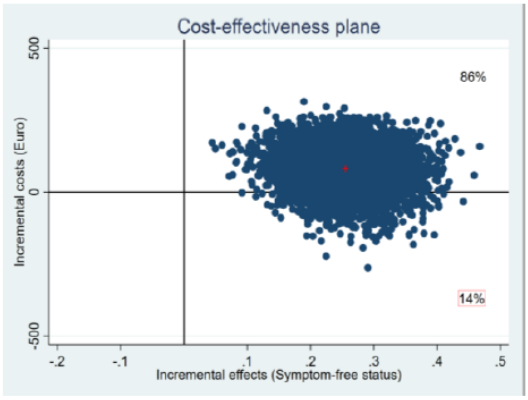
Societal perspective

Table 4 shows the incremental costs, effects, and ICERs based on the 5000 bootstraps. The IMI dominated the WLC related to symptom-free status with larger effects on the SPS and SIAS, respectively, and less costs (SPS, €-321 CI 95% [−862, 66]; SIAS, €-324 CI 95% [−774, 125]). In the cost-effectiveness plane, the majority of ICERs fell under the southeast quadrant (Figure 1), indicating a 92% probability that the intervention produces greater health effects at lower costs than WLC (Figure 2).

The IMI generated small QALY gains at lower costs (€-319, 95% CI, −831–64) compared with WLC. From a societal perspective, 93% of the simulated ICERs fell under the southeast quadrant reflecting the intervention's probability of dominating WLC (Figure 3). Assuming a WTP of €1,000 for QALY gains, the probability rose to 95% (Figure 4).

Healthcare perspective

The bootstrapped ICER for symptom-free status on the SPS and SIAS yielded an ICER of €348 (95% CI, SPS [−284,1069]; SIAS [304, 1043]), indicating that the IMI generated larger effects at higher costs (SPS, €81; SIAS, €79) compared with WLC. Hence, the majority of ICERs fell under the northeast quadrant (86%), while the probability of cost-effectiveness of the intervention than that of WLC rose from 70/69% at a WTP of €500 to 97% at a WTP of €1000 (Figure 2). Regarding the cost-utility, the



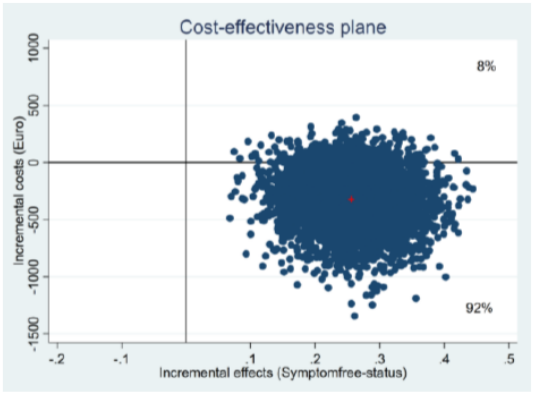
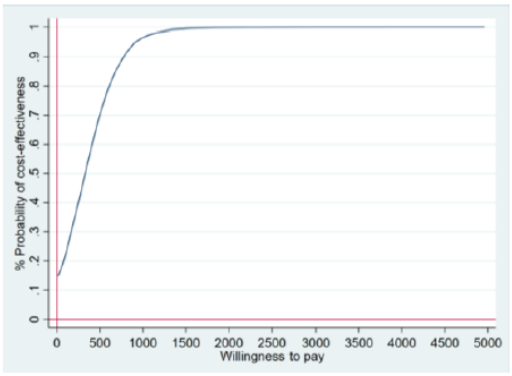


Figure 1 Scatter plot showing the mean differences in costs and effect outcome (symptom-free status, SPS) data using 5000 bootstrap replications from healthcare (left) and societal (right) perspective



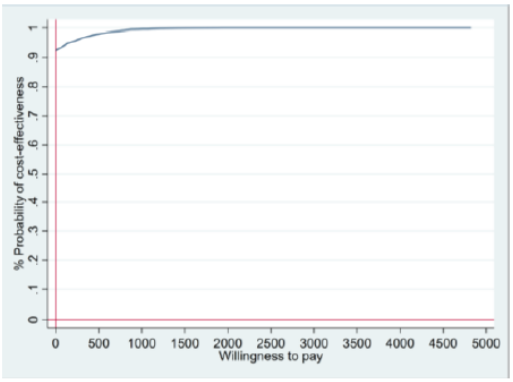
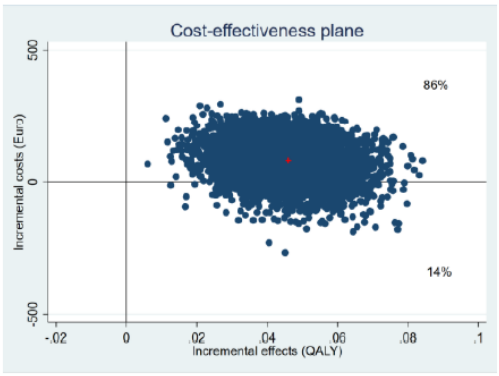


Figure 2 Cost-effectiveness acceptability curve showing the probability of the IMI being cost-effective at varying WTP ceilings (based on 5000 replicates of the ICER using mean differences in costs and symptom-free status based on SPS) from healthcare (left) and societal (right) perspective



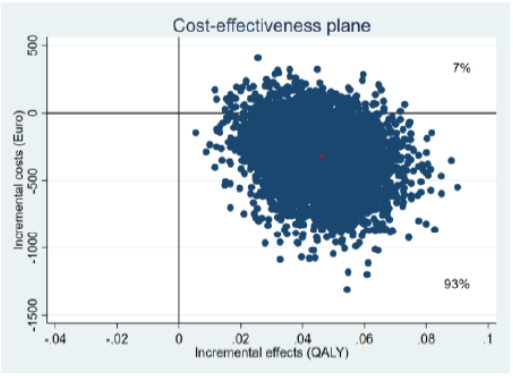
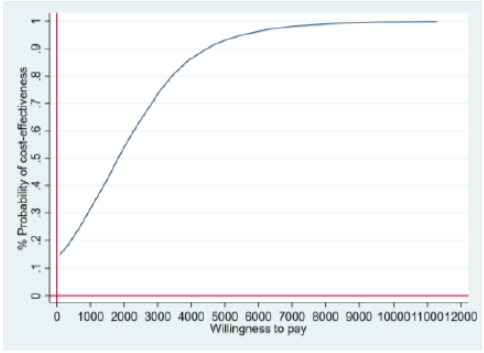


Figure 3 Scatter plot showing the mean differences in costs and effect outcome (AQoL QALY) data using 5000 bootstrap replications from healthcare (left) and societal (right) perspective



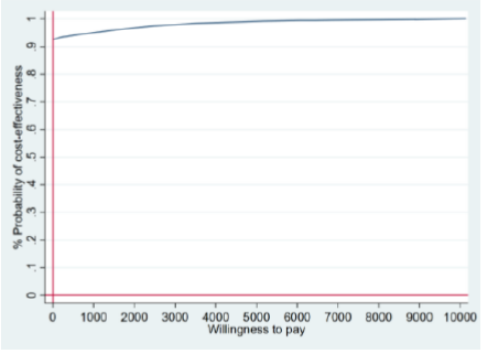


Figure 4 Cost-effectiveness acceptability curve showing the probability of the IMI being cost-effective at varying WTP ceilings (based on 5000 replicates of the ICER incremental cost-effectiveness ratio using mean differences in costs and QALYs) from healthcare (left) and societal (right) perspective.

IMI generated higher effects per QALY gained at higher costs compared with WLC (€81; 95% CI, 105–200). Thus, 86% of the simulated ICERs fell in the northeast quadrant, indicating higher costs and QALY gains. Assuming a WTP of €0; €2,000; and €6,000 for gaining one QALY, the probability rose from 14% to 54% to 96% (Figure 4).

Sensitivity analyses

First, the study completers generated significant effects on all assessed outcomes and effect sizes at least as large as in the ITT analysis (±*d* = 0.1). Second, regarding the QALY gains, even increasing the invention costs by 50% and 100%, respectively, did not alter the interpretation of results neither from a societal nor healthcare perspective (Table 2). Third, excluding the Swiss students did not affect the results of the CEA nor the CUA analyses. Fourth, using the EQ-5D-5L resulted in a slightly non-significant (t_{200} = −0.65, *P* = 0.52) incremental QALY gain in favor of the IMI (0.939 QALY, SD 0.070) compared with WLC (0.932 QALY, SD 0.865). The greater sensitivity of the AQoL instrument and the potential ceiling effect of the EQ-5D instrument may have led to the differences between the AQoL QALYs (>0.55) and the EQ-5D QALYs (>0.9) Nevertheless, for gaining a QALY at a WTP of €0/€10,000, the probability of cost-effectiveness was similar (99%/89%) from societal perspective and lower (15%/26%) from a healthcare perspective compared with the AQoL QALYs. Fifth, using the diagnostic status for the health economic evaluation yielded similar results to the symptom-free status (Table 1).

Discussion

Principal findings

This study is the first to evaluate the long-term efficacy and the cost-effectiveness of an unguided IMI for university students with SAD compared with waitlist control condition (WLC) with unrestricted access to treatment as usual over 6 months from a societal and public healthcare perspective. The IMI maintained a significant and favorable effect on social phobia symptoms with moderate to large effect sizes between groups at follow-up assessment (6 months; SPS, *d* = 0.83; SIAS, *d* = 0.59) compared with WLC. The IMI generated slightly lower costs (€-321; 95% CI, −862–66), more QALYs (0.046; 95% CI, 0.024–0.68), and symptom-free status (SPS = 0.26; 95% CI, 0.15–0.37) compared with WLC in the long-term. From a societal perspective, the IMI dominated the WLC, while from a healthcare perspective, the probability for cost-effectiveness was 96% at a WTP of €6,000 (US$ 7,956) per symptom-free status and QALY. Our findings were robust to sensitivity analyses.

Comparison with prior work

Our findings are consistent with the evidence on the efficacy of unguided IMIs in the general population suffering from SAD in the long-term.[18] A study (N = 81) compared an unguided IMI with two types of guided self-help after 6 months[81] and found within-group effects (*d* ≈1.5) similar to our study, but no significant effect was observed between the groups. Likewise, smaller but also persistent effects (d = 0.2) of an unguided IMI were found when compared with WLC after one year.[28]

Regarding the university students, our findings support the existing evidence for internet-based interventions targeting SAD showing similar results as the previous studies[23] (some focusing on fear of public speaking[22,24]). Furthermore, these studies are characterized by the substantial dropout rate at post-treatment ([23], 40%) or follow-up (24,67%) and did not assess the long-term efficacy of the intervention.

Likewise, further research is needed to confirm the economic benefits of IMIs for SAD. Results from our trial add

to the converging evidence pointing to their cost-effectiveness. Four studies reported on the health economic outcomes of IMIs in SAD.[25–28] Three studies found that guided IMIs might be a cost-effective approach compared with an active control over a period of 6 months and 4 years from a societal and provider perspective, respectively. Showing similar results to our study, one guided IMI generated less costs and better treatment outcomes. At a WTP of 0 Euro, this IMI showed an 81% probability of cost-effectiveness at 6 months[25] and a 61% probability at a 4-year follow-up[26]. Another guided IMI compared with face-to-face treatment was judged cost-effective, only including cost for therapist time.[27]

To our knowledge, only one health economic evaluation has compared unguided IMI and passive control,[28] which indicated that the intervention is likely to be cost-effective. The study differs from the present study in terms of the general population, higher average age, different inclusion criteria (also subclinical participants), and instruments used (SF-6D versus AQoL). The IMI generated higher costs and better effects at 6 months and dominated the control condition after 12 months. Compared with our study, this trial focused on a non-clinical sample and had a substantial dropout rate (50%) which could lead to selection bias by attrition.

Strengths and limitations

This study has several strengths and limitations. The data in our trial was based on self-report measures and diagnostic interviews, thereby increasing the robustness of the results while minimizing bias accompanying self-reported data due to recall period or selective recall. Additionally, our study only showed a relatively small number of dropouts (22.5%) at 6-month follow-up compared with most unguided studies.[82] This could be due to our structured research process (e.g., diagnostic interviews) and highly educated and technologically sophisticated group of participants. Moreover, the characteristics of the study groups were well balanced at baseline, and the proportion of female participants (62%) was relatively low compared with most IMIs also reflecting the distribution of SAD in the population. A further strength of our study is the inclusion of a full economic evaluation. Notably, the economic findings were consistent across various sensitivity analyses.

However, several limitations were noted. First, the time horizon of our study was limited to 6 months. Costs due to present and future underachievement, prolonged studies, and study dropouts resulting in lower academic qualifications could not be captured nor included in our evaluations and may even increase the impact of the intervention. Third, most instruments were based on self-reported measures, which might have led to "social desirability" and "recall bias." Fourth, high structuring and research attention, e.g., diagnostic interviews at the end of the 6-month period of our study, could have led to the overestimation of effects compared with interventions in routine care due to the Hawthorne effect.[83] Fifth, the generalizability of our findings is limited to similar settings. Thus, our results may be applicable to university students in Western countries with similar study characteristics. Finally, in health economic evaluations[84], a standard care comparator (e.g., face-to-fact CBT) is recommended rather than a waitlist control group to avoid potential nocebo effects.[85]

Clinical implications and future research

The study results support the idea that IMIs could be a low-threshold, effective and affordable way to reduce the adverse effects of social anxiety disorder. The advantage of an IMI is that compared with standard therapies the marginal cost decreases when extending coverage or increasing the uptake of the intervention.[86] Low marginal costs and the scalability of IMIs enable them to be used as public health tools to generate effects at the population level compared with guided or face-to-face treatments that are not as scalable.

Moreover, based on the nature of social anxiety disorder, patients tend to avoid face-to-face contact to therapist as they fear to be negatively evaluated. IMIs offer a low-threshold approach to help those affected without using face-to-face (F2F) treatments. This preference may also increase the use of unguided approaches compared with standard therapies. Therefore, future research should evaluate head-to-head comparisons of self-help IMIs with guided IMIs and F2F treatments.

Furthermore, in our study, only students who met the diagnostic criteria were included. Nevertheless, the students who were interested in participating but showing subclinical symptoms of SAD increased threefold. Thus, further research is needed to investigate its preventive effect in students at risk of developing SAD. The application of this IMI across the range of mild to severe symptoms of SAD may better fit the requirements of a student mental health service at a university. However, under uncontrolled naturalistic conditions, the lack of research attention and reminders may decrease the effectiveness of unguided IMIs. Implementation studies could further examine the uptake and effectiveness of unguided IMIs under routine care conditions.

The German SAD treatment guideline[87] recommends IMIs based on cognitive-behavioral therapy to bridge the waiting times or accompanying face-to-face treatment. Moreover, the results of our study add to the emerging evidence base in support of recommending IMIs as a viable treatment option in clinical guidelines. An official recognition of IMIs as a treatment option for SAD would help bridge the current treatment gap. During the COVID-19 pandemic, the barriers of treatment utilization increase and SAD symptoms in students maintain due to minimal social contact and isolation.[88] Untreated persons

generate long-term costs caused by persistent social anxiety symptoms, such as low academic performance, subsequent study dropouts, and worse job prospects, which are not included in our health economic evaluation. Thus, larger studies with longer follow-up periods are needed in the future to investigate the full extent of SAD from a cost viewpoint.

Conclusion

This study strengthens the existing evidence confirming that internet-based self-help interventions for SAD can generate and sustain a significant and favorable effect in reducing social anxiety symptoms in a cost-effective way. Given the positive effects of the intervention, the implementation of this IMI as part of a student's healthcare management at the university would be essential.

Key points

Unguided internet- and mobile-based interventions can induce and maintain favorable effects in students with social anxiety disorder over a period of 6 months.

The mobile interventions have an acceptable likelihood of cost-effectiveness.

It would be worthwhile to integrate such mobile interventions into routine mental healthcare at universities.

Acknowledgments

The authors gratefully acknowledge the contribution of all participants, research assistants such as Julia Burger, Mirjam Thomas, therapists and all others who contributed to our study.

Author Contributions

FK, DDE, TB have contributed to the study design. FK drafted the manuscript. CB and FS contributed to the analysis and interpretation of the data. CB, DDE, FS, HB, TB critically revised the content. All authors read and approved the final manuscript.

Competing Interests

DDE has served as a consultant to/on the scientific advisory boards of Sanofi, Novartis, Minddistrict, Lantern, Schoen Kliniken, Ideamed and German health insurance companies (BARMER, Techniker Krankenkasse) and a number of federal chambers for psychotherapy. He is also stakeholder in the Institute for health training online (formerly GET.ON, now HelloBetter), which aims to implement scientific findings related to digital health interventions into routine care. HB received consultancy fees, reimbursement of congress attendance and travel costs as well as payments for lectures from psychotherapy, psychiatry and further medical associations, institutes, clinics, and companies in the context of e-mental-health topics. He sublicensed a digital intervention to a company providing digital health interventions. He has been the beneficiary of study support (third-party funding) from several public funding organizations. The other authors CB, FK and FS, TB declare no competing interest.

Data Availability Statement

The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

Funding

Funding was received from the BARMER GEK (German statutory health insurance company). The funders did not have a role in study design; data collection, analyze the interpretation of results, or the decision to publicize the study results. DDE and HB obtained the funding for this trial.

References

1 Farrer, L. *et al.* Technology-based interventions for mental health in tertiary students: Systematic review. *J. Med. Internet Res.* **15**, (2013).

2. Jacobi, F. *et al.* Twelve-months prevalence of mental disorders in the German Health Interview and Examination Survey for Adults–Mental Health Module (DEGS1-MH): a methodological addendum and correction. *Int. J. Methods Psychiatr. Res.* **24**, 305–313 (2015).

3. Baldauf, M., Thomas, A. & Strau, B. [Symptoms of social phobia and their relationship to interpersonal characteristics in a sample of German medical students]. *Psychother. Psychosom. Med. Psychol.* **64**, 76–81 (2014).

4. Gültekin, B. K., Dereboy, I. F. & Dereboy, F. The prevalence of social phobia, and its impact on quality of life, academic achievement, and identity formation in university students. *Turk Psikiyatr. Derg.* **22**, 150–158 (2011).

5. Gilles, D. M., Turk, C. L. & Fresco, D. M. Social anxiety, alcohol expectancies, and self-efficacy as predictors of heavy drinking in college students. *Addict. Behav.* **31**, 388–398 (2006).

6. Olfson, M. *et al.* Barriers to the treatment of social anxiety. *Am. J. Psychiatry* **157**, 521–527 (2000).

7. Tillfors, M. & Furmark, T. Social phobia in Swedish university students: prevalence, subgroups and avoidant behavior. *Soc. Psychiatry Psychiatr. Epidemiol.* **42**, 79–86 (2007).

8. Cranford, J. A. *et al.* Major Differences: Variations in Undergraduate and Graduate Student Mental Health and Treatment Utilization Across Academic Disciplines. *J. Am. Coll. Heal.* **61**, 23–41 (2016).

9. Kessler, R. C. The impairments caused by social phobia in the general population: implications for intervention. *Acta Psychiatr. Scand.* **108**, 19–27 (2003).

10. Magee, W. J., Eaton, W. W., Wittchen, H.-U., McGonagle, K. A. & Kessler, R. C. Agoraphobia, simple phobia, and social phobia in the National Comorbidity

Survey. *Arch. Gen. Psychiatry* **53**, 159–168 (1996).
11. Stuhldreher, N. *et al.* The costs of social anxiety disorder: The role of symptom severity and comorbidities. *J. Affect. Disord.* **165**, 87–94 (2014).
12. DJ, D. & AB, D. Campus suicide prevention: bridging paradigms and forging partnerships. *Harv. Rev. Psychiatry* **20**, 209–221 (2012).
13. Ebert, D. D. *et al.* Barriers of mental health treatment utilization among first year college students: First cross-national results from the WHO World Mental Health International College Student Initiative. *Int. J. Methods Psychiatr. Res.* **28**, e1782 (2019).
14. Chartier, M. J., Hazen, A. L. & Stein, M. B. Lifetime patterns of social phobia: a retrospective study of the course of social phobia in a nonclinical population. *Depress. Anxiety* **7**, 113–121 (1998).
15. Berger, T. & Andersson, G. Internetbasierte Psychotherapien: Besonderheiten und empirische Evidenz. *PPmP - Psychother. Psychosom. Medizinische Psychol.* **59**, 159–170 (2009).
16. Ebert, D. D. *et al.* Internet- and Mobile-Based Psychological Interventions: Applications, Efficacy, and Potential for Improving Mental Health. *Eur. Psychol.* **23**, 167–187 (2018).
17. Ebert, D. D., Cuijpers, P., Muñoz, R. F. & Baumeister, H. Prevention of Mental Health Disorders Using Internet- and Mobile-Based Interventions: A Narrative Review and Recommendations for Future Research. *Front. Psychiatry* **8**, 1–16 (2017).
18. Kampmann, I. L., Emmelkamp, P. M. G. & Morina, N. Meta-analysis of technology-assisted interventions for social anxiety disorder. *J. Anxiety Disord.* **42**, 71–84 (2016).
19. El Alaoui, S., Hedman, E., Ljótsson, B. & Lindefors, N. Long-term effectiveness and outcome predictors of therapist-guided internet-based cognitive-behavioural therapy for social anxiety disorder in routine psychiatric care. *BMJ Open* **5**, (2015).
20. Hedman, E. *et al.* A 5-Year Follow-up of Internet-Based Cognitive Behavior Therapy for Social Anxiety Disorder. *J. Med. Internet Res.* **13**, (2011).
21. Berger, T., Hohl, E. & Caspar, F. Internetbasierte Therapie der sozialen Phobie: Ergebnisse einer 6-Monate-Katamnese. *Z. Klin. Psychol. Psychother.* **39**, 217–221 (2010).
22. Tillfors, M. *et al.* Treating university students with social phobia and public speaking fears: internet delivered self-help with or without live group exposure sessions. *Depress. Anxiety* **25**, 708–717 (2008).
23. McCall, H. C., Richardson, C. G., Helgadottir, F. D. & Chen, F. S. Evaluating a Web-Based Social Anxiety Intervention Among University Students: Randomized Controlled Trial. *J. Med. Internet Res.* **20**, (2018).
24. Botella, C. *et al.* An Internet-Based Self-Help Treatment for Fear of Public Speaking : A Controlled Trial. *Cyberpsychology, Behav. Soc. Netw.* **13**, (2010).
25. Hedman, E. *et al.* Cost-effectiveness of Internet-based cognitive behavior therapy vs. cognitive behavioral group therapy for social anxiety disorder: Results from a randomized controlled trial. *Behav. Res. Ther.* **49**, 729–736 (2011).
26. Hedman, E. *et al.* Clinical effectiveness and cost-effectiveness of Internet- vs. group-based cognitive behavior therapy for social anxiety disorder: 4-year follow-up of a randomized trial. *Behav. Res. Ther.* **59**, 20–29 (2014).
27. Titov, N., Andrews, G., Johnston, L., Schwencke, G. & Choi, I. Shyness programme: longer term benefits, cost-effectiveness, and acceptability. *Aust. N. Z. J. Psychiatry* **43**, 36–44 (2009).
28. Powell, J. *et al.* Effectiveness and Cost-Effectiveness of a Self-Guided Internet Intervention for Social Anxiety Symptoms in a General Population Sample: Randomized Controlled Trial. *J. Med. Internet Res.* **22**, e16804 (2020).
29. Kählke, F. *et al.* Efficacy of an unguided internet-based self-help intervention for social anxiety disorder in university students: A randomized controlled trial. *Int. J. Methods Psychiatr. Res.* **28**, e1766 (2019).
30. Kählke, F. *et al.* Efficacy and cost-effectiveness of an unguided, internet- and mobile-based self-help intervention for social anxiety disorder in university students: protocol of a randomized controlled trial. *BMC Psychiatry* **19**, 197 (2019).
31. Datinf GmbH. Randlist. Software to create Randomisations Lists. (2018).
32. Questback GmbH. EFS Survey, Version Summer 2017. (2017).
33. Rohde, P., Lewinsohn, P. M. & Seeley, J. R. Comparability of Telephone and Face-to-Face Interviews in Assessing Axis I and II Disorders. *Am. J. Psychiatry* **154**, 1593–1598 (1997).
34. Clark, D. & Wells, A. *A cognitive model of social phobia*. (Guilford Press, 1995).
35. Berger, T. *et al.* Behaviour Research and Therapy Internet-based treatment of social phobia : A randomized controlled trial comparing unguided with two types of guided self-help. *Behav. Res. Ther.* **49**, 158–169 (2011).
36. Weeks, J. W. & Howell, A. N. The Bivalent Fear of Evaluation Model of Social Anxiety: Further Integrating Findings on Fears of Positive and Negative Evaluation. *Cogn. Behav. Ther.* **41**, 83–95 (2012).
37. Stangier, U., Heidenreich, T., Berardi, A., Golbs, U. & Hoyer, J. Die Erfassung sozialer Phobie durch die Social Interaction Anxiety Scale (SIAS) und die Social Phobia Scale (SPS). *Z. Klin. Psychol. Psychother.* **28**, 28–36 (1999).
38. Mattick, R. P. & Clarke, J. C. Development and validation of measures of social phobia scrutiny fear and social interaction anxiety11Editor's note: This article was written before the development of some contemporary measures of social phobia, such as the Social Phobia and Anxiety Inve. *Behav. Res. Ther.* **36**, 455–470 (1998).
39. Heinrichs, N. *et al.* Validität und Reliabilität der Social Interaction Anxiety Scale (SIAS) und der Social Phobia Scale (SPS). *Verhaltenstherapie* **12**, 26–35 (2002).
40. Jacobson, N. S. & Truax, P. Clinical significance: A statistical approach to defining meaningful change in psychotherapy research. *J. Consult. Clin. Psychol.* **59**, 12–19 (1991).
41. Stangier, U. & Heidenreich, T. *Die Liebowitz Soziale Angst-Skala (LSAS). Internationale Skalen für*

Psychiatrie (Hogrefe, 2003).
42. Fergus, T. A. *et al.* The Fear of Positive Evaluation Scale: Psychometric properties in a clinical sample. *J. Anxiety Disord.* **23**, 1177–1183 (2009).
43. Weeks, J. W., Heimberg, R. G., Rodebaugh, T. L. & Norton, P. J. Exploring the relationship between fear of positive evaluation and social anxiety. *J. Anxiety Disord.* **22**, 386–400 (2008).
44. Weeks, J. W. The Disqualification of Positive Social Outcomes Scale: A novel assessment of a long-recognized cognitive tendency in social anxiety disorder. *J. Anxiety Disord.* **24**, 856–865 (2010).
45. Hautzinger, M., Keller, F. & Kühner, C. *Beck Depressions-Inventar (BDI-II)*. (Harcourt Test Services, 2006).
46. Schlarb, A. & Hautzinger, M. Klinisch-psychiatrische Ratingskalen für das Kindes-und Jugendalter. *Göttingen: Hogrefe* (2011).
47. Franke, G. BSI, Brief Symptom Inventory von L. R. Derogatis (Kurzform der SCL-90-R) - deutsches Manual. *Beltz Test GmbH* (2000).
48. Horowitz, L., Rosenberg, S. E., Baer, B. A., Ureño, G. & Al, E. Inventory of interpersonal problems: Psychometric properties and clinical applications. *J. Consult. Clin. Psychol.* **56**, 885–892 (1988).
49. Horowitz, L., Strauß, B. & Kordy, H. *Inventar zur Erfassung interpersonaler Probleme: IIP-D; deutsche Version*. (Beltz., 2000).
50. Richardson, J., Iezzi, A., Khan, M. A. & Maxwell, A. Validity and Reliability of the Assessment of Quality of Life (AQoL)-8D Multi-Attribute Utility Instrument. *Patient - Patient-Centered Outcomes Res.* **7**, 85–96 (2014).
51. Sonntag, M. *et al.* Reliability, validity and responsiveness of the EQ-5D in assessing and valuing health status in patients with social phobia. *Heal. Qual Life Outcomes* **11**, 215 (2013).
52. Ludwig, K., Graf von der Schulenburg, J. M. & Greiner, W. German Value Set for the EQ-5D-5L. *Pharmacoeconomics* **36**, 663–674 (2018).
53. Richardson, J., Sinha, K., Iezzi, A. & Khan, M. A. Modelling utility weights for the Assessment of Quality of Life (AQoL)-8D. *Qual. Life Res.* **23**, 2395–2404 (2014).
54. Hakkaart-van Roijen, L., Van Straten, A., Donker, M. & Tiemens, B. Trimbos/iMTA questionnaire for costs associated with psychiatric illness (TIC-P). *Rotterdam Inst. Med. Technol. Assess.* (2002).
55. Bouwmans, C. *et al.* Feasibility, reliability and validity of a questionnaire on healthcare consumption and productivity loss in patients with a psychiatric disorder (TiC-P). *BMC Health Serv. Res.* **13**, 217 (2013).
56. Nobis, S. *et al.* Efficacy and cost-effectiveness of a web-based intervention with mobile phone support to treat depressive symptoms in adults with diabetes mellitus type 1 and type 2 : design of a randomised controlled trial. *BMC Psychiatry* **13**, 1 (2013).
57. Buntrock, C. *et al.* Preventing Depression in Adults With Subthreshold Depression : Health-Economic Evaluation Alongside a Pragmatic Randomized Controlled Trial of a Web-Based Intervention Corresponding Author : *J. Med. Internet Res.* **19**, 1–16 (2017).
58. Bock, J.-O. *et al. Standardisierte Bewertungssätze aus gesellschaftlicher Perspektive für die gesundheitsökonomische Evaluation*. vol. 55 (Nomos Verlagsgesellschaft mbH & Co. KG, 2015).
59. GmbH, L.-F. Die LAUER-Taxe. (2016).
60. Destatis. Consumer Price Indices. . (2015).
61. Drummond, M., Sculpher, M. J., Claxton, K., Stoddart, G. L. & Torrance, G. W. *Methods for the Economic Evaluation of Health Care Programmes*. (Oxford University Press, 2015).
62. Osterhaus, J. T., Gutterman, D. L. & Plachetka, J. R. Healthcare resource and lost labour costs of migraine headache in the US. *Pharmacoeconomics* **2**, 67–76 (1992).
63. Matthews, J. N., Altman, D. G., Campbell, M. J. & Royston, P. Analysis of serial measurements in medical research. *BMJ* **300**, 230–235 (1990).
64. Shemilt, I., Thomas, J. & Morciano, M. A web-based tool for adjusting costs to a specific target currency and price year. *Evid. Policy* **6**, 51–59 (2010).
65. Kählke, F. *et al.* Efficacy and cost-effectiveness of an unguided, internet-based self-help intervention for social anxiety disorder in university students: Protocol of a randomized controlled trial. *BMC Psychiatry* **19**, (2019).
66. Schulz, K. F., Altman, D. G. & Moher, D. CONSORT 2010 Statement: updated guidelines for reporting parallel group randomised trials. *BMJ* **340**, (2010).
67. Little, R. J. A. & Rubin, D. B. Statistical analysis with missing data. *Stat. Anal. with Missing Data* 1–381 (2014) doi:10.1002/9781119013563.
68. Corp., I. IBM Corp. Released 2017. IBM SPSS Statistics for Windows, Version 25.0. (2017).
69. Field, A. Andy Field - Discovering Statistics Using IBM SPSS Statistics. *Lavoisier.Fr* 1–816 (2013).
70. Shi, Q., Pavey, E. S. & Carter, R. E. Bonferroni-based correction factor for multiple, correlated endpoints. *Pharm. Stat.* (2012) doi:10.1002/pst.1514.
71. Altman, D. G. Confidence intervals for the number needed to treat. *BMJ* **317**, 1309–1312 (1998).
72. Cook, R. J. & Sackett, D. L. The number needed to treat: a clinically useful measure of treatment effect. *BMJ* **310**, 452–454 (1995).
73. Husereau, D. *et al.* Consolidated Health Economic Evaluation Reporting Standards (CHEERS) statement. *BMC Med.* **11**, (2013).
74. Ramsey, S. D. *et al.* Cost-Effectiveness Analysis Alongside Clinical Trials II—An ISPOR Good Research Practices Task Force Report. *Value Heal.* **18**, 161–172 (2015).
75. Dixon, W. J. & Yuen, K. K. Trimming and winsorization: A review. *Stat. Hefte* **15**, 157–170 (1974).
76. Hout, B. A. Van, Al, M. J., Gordon, G. S. & Rutten, F. F. H. Costs, effects and C/E-ratios alongside a clinical trial. *Health Econ.* **3**, 309–319 (1994).
77. Briggs, A. H. & Gray, A. M. Handling Uncertainty in Economic Evaluation. *The Advanced Handbook of Methods in Evidence Based Healthcare* 314–337 doi:10.4135/9781848608344.n18.
78. Willan, A. R., Briggs, A. H. & Hoch, J. S. Regression methods for covariate adjustment and subgroup analysis for non-censored cost-effectiveness data.

Health Econ. **13**, 461–475 (2004).

79. StataCorp. 2019. Stata Statistical Software: Release 16. College Station, TX: StataCorp LLC.
80. Landis, J. R. & Koch, G. G. The Measurement of Observer Agreement for Categorical Data. *Biometrics* **33**, 159–174 (1977).
81. Berger, T. *et al.* Internet-based treatment of social phobia: A randomized controlled trial comparing unguided with two types of guided self-help. *Behav. Res. Ther.* **49**, 158–169 (2011).
82. Van Ballegooijen, W. *et al.* Adherence to Internet-based and face-to-face cognitive behavioural therapy for depression: a meta-analysis. *PLoS One* **9**, e100674 (2014).
83. Abraham, M. B. *et al.* The Importance of the Hawthorne Effect on Psychological Outcomes Unveiled in a Randomized Controlled Trial of Diabetes Technology. *J. Diabetes Sci. Technol.* **12**, 735–736 (2018).
84. Sacristán, J. A., Abellán-Perpiñán, J. M., Dilla, T., Soto, J. & Oliva, J. Some reflections on the use of inappropriate comparators in CEA. *Cost Eff. Resour. Alloc.* **18**, (2020).
85. Furukawa, T. A. *et al.* Waiting list may be a nocebo condition in psychotherapy trials: a contribution from network meta-analysis. *Acta Psychiatr. Scand.* **130**, 181–192 (2014).
86. Gomes, M., Murray, E. & Raftery, J. Economic Evaluation of Digital Health Interventions: Methodological Issues and Recommendations for Practice. *Pharmacoeconomics* **40**, 367–378 (2022).
87. Bandelow, B. *et al. S3-Leitlinie Behandlung von Angststörungen: Version 2.* https://www.awmf.org/leitlinien/detail/ll/051-028.html (2021).
88. Xiong, J. *et al.* Impact of COVID-19 pandemic on mental health in the general population: A systematic review. *J. Affect. Disord.* **277**, 55–64 (2020).
89. Bock, J.-O. *et al.* Ermittlung standardisierter Bewertungssätze aus gesellschaftlicher Perspektive für die gesundheitsökonomische Evaluation. *Das Gesundheitswes.* **77**, 53–61 (2014).

Table 1 Results of the ANCOVAs and *Cohen's d* for the primary and secondary outcome measures (ITT sample) at 6 months follow-up (T3)

	T3 Between-groups effect			T3 Within-group effect	T3 Within-group effect
	d (95% CI)			IG	WLC
Outcome		$F_{1,197}$	*p*		
Primary outcome					
SPS	0.83 (0.54; 1.1)	55.01	<.001	1.27 (0.96; 1.57)	0.38 (0.10; 0.66)
SIAS	0.59 (0.30; 0.87)	49.03	<.001	1.30 (0.99; 1.60)	0.39 (0.11; 0.67)
Secondary Outcome					
BDI-II	0.45 (0.17; 0.73)	7.21	<.001	0.59 (0.31; 0.87)	0.17 (-0.11; 0.44)
BSI	0.38 (0.10; 0.66)	7.41	<.001	0.52 (0.24; 0.81)	0.17 (0.11; 0.45)
LSAS	0.76 (0.47; 1.05)	54.92	<.001	1,30 (1.00; 1.61)	0.37 (0.09; 0.65)
IIP-64	0.60 (0.32; 0.89)	44.92	<.001	1.16 (0.86; 1.46)	0.32 (0.04; 0.60)
FPES	0.54 (0.26; 0.82)	40.22	<.001	0.94 (0.65; 1.23)	-0.01 (-0.27; 0.29)
DPSOS-Self	0.56 (0.82; 0.55)	21.43	<.001	0.68 (0.40; 0.97)	-0.06 (-0.34; 0.22)
DPSOS-Others	0.58 (0.30; 0.86)	31.27	<.001	0.80 (0.51; 1.09)	-0.01 (-0.29; 0.27)
AQol	0.23 (0.50; 0.05)	3.92	<0.01	0.66 (0.38; 0.95)	0.32 (0.04; 0.59)
EQ-5D	-0.08 (-0.36; 0.20)	2.14	>0.05	0.14 (-0.14; 0.42)	0.15 (-0.13; 0.42)

The Analysis of covariance with baseline levels as covariates (at T0) was used

ANCOVA Analysis of variance, *IG* intervention group, *ITT* intention-to-treat, *M* means, *SD* standard deviation, *WLC* waitlist control group

Table 2 Means and standard deviations for the IG and the WLC group (ITT sample)

	T0				T1[a]				T2 [a]			
	IG		WLC		IG		WLC		IG		WLC	
Outcome	M	SD	M	SD	M	SD	M	SD	M	SD	M	SD
Primary outcome												
SPS	34.36	11.79	35.71	13.54	21.03	11.54	30.63	13.72	19.48	11.61	30.32	14.38
SIAS	51.47	11.23	48.71	12.92	36.72	13.86	44.36	14.05	35.10	13.78	43.40	14.39
Secondary outcome												
BDI-II	12.68	8.23	12.97	7.71	8.12	6.71	11.88	8.16	8.43	5.94	11.65	8.17
BSI	0.86	0.49	0.92	0.56	0.56	0.40	0.81	0.57	0.62	0.42	0.82	0.60
LSAS	77.61	16.87	76.96	19.57	58.82	20.45	72.51	22.17	52.08	21.87	69.10	22.64
IIP-64	1.71	0.39	1.66	0.43	1.34	0.47	1.5	0.48	1.17	0.53	1.5	0.56
FPES	43.82	11.00	39.90	13.00	36.17	13.49	39.95	14.6	33.19	11.54	40.06	13.62
DPSOS-Self	16.76	4.91	15.85	5.68	14.35	5.42	16.06	5.89	13.47	4.69	16.16	4.89
DPSOS-Others	42.51	11.93	40.16	12.56	36.11	14.81	40.60	14.81	32.27	13.59	40.31	14.03
AQol	0.57	0.14	0.58	0.17	0.68	0.16	0.61	0.18	0.67	0.16	0.63	0.19
EQ5D	0.94	0.08	0.92	0.11	0.95	0.08	0.93	0.11	0.93	0.09	0.93	0.09

[a] Missing data imputed by multiple imputation

IG intervention group, *ITT* intention-to-treat, *M* means, *SD* standard deviation, *WLC* waitlist control group

Table 3 Average costs per participant (in €) by condition at 6-months follow-up

	IG (n=100)		**WLC** (n=100)		Incremental costs
	Mean (SD), €		Mean (SD), €		Difference, €
Intervention	178.50		-	-	**+178.50**
Healthcare costs					
Physician services	18.90	(39.59)	38.06	(104.37)	-19.16
Mental Healthcare	114.31	(294.02)	84.81	(215)	+29.50
Inpatient care	0	(0)	21.97	(154.57)	-21.97[a]
Day care	0	(0)	47.42	(474.25)	-47.42
Non-physician services	12.58	(36.61)	24.93	(136.43)	-12.35
Prescription drugs	21.70	(77.65)	23.11	(114.84)	-1.40
	167.49	(333.33)	240.31	(679.24)	**-72.82**
Patient and family costs					
Over the counter drugs	19.52	(36.08)	30.36	(64.13)	-10.83
Opportunity costs	61.78	(131.52)	130.27	(364.33)	-68.49
Travel expenses	8.67	(22.84)	19.10	(84.96)	-10.42
Domestic help /informal care	22.97	(92.16)	23.46	(131.93)	-0.49
	112.95	(220.88)	203.19	(475.86)	**-90.24**
Productivity losses					
Absenteeism (work)	219.48	(405.15)	203.13	(568.15)	+16.35
Presenteeism (work)	172.06	(331.87)	415.30	(1013.47)	-243.24
	391.54	(676.38)	618.43	(1466.64)	**-226.89**
Total healthcare costs	345.99	(333.33)	240.31	(679.24)	**+105.69**
Total societal costs	850.49	(943.42)	1061.94	(1969.21))	**-211.45**[b]
Sensitivity analyses					
Absenteeism (studies)	500.69	(591.80)	723.52	(1057.56)	-222.83
Presenteeism (studies)	320.84	(354.25)	348.88	(476.02)	-28.04
	821.53	(789.47)	1072.40	(1370.93)	-250.87

Average costs per participant are based on the area under the curve approach and an intention-to-treat-sample (N=200)

[a]Costs included one outlier that was handled using Winsorizing
[b]Numbers presented may not add up precisely to the totals provided due to rounding

IG intervention group, *WLC* waitlist control group,

Table 4 Results of the main and sensitivity analysis based on 5000 bootstrap simulations

Main Analysis	**Outcome**	**Incremental costs** € (95% CI)	**Incremental effects** Points (95% CI)	**ICER** €/Points (95% CI)	**Distribution over the CE-plane (%)**				**WTP (%)**
					NE[b]	**SE**[c]	**SW**[d]	**NW**[e]	
Societal perspective	Symptom-free status **SPS** (range: 0-1)	-321 (-862 to 66)	0.26 (0.15 to 0.37) **	Dominant (to 414)	8	92	-	-	0 (0.92); 500 (0.98); 1,000 (1)
	Symptom-free status **SIAS** (range: 0-1)	-324 (-774 to 125)	0.24 (0.14 to 0.34) **	Dominant (to 415)	8	92	-	-	0 (92); 500 (0.98); 1,000 (1)
	AQoL QALYs (range: 0-1)	-319 (-831 to 64)	0.046** (0.024 to 0.68)	Dominant (to 2447)	7	93	-	-	0 (0.93); 1,000 (0.95); 2,000 (0.97); 3,000 (0.98); 10,000 (1)
Healthcare perspective	Symptom-free status **SPS** (range: 0-1)	81 (-105 to 200)	0.255 (0.144 to 0.366) **	348 (-284 to 1069)	86	14	-	-	0 (0.14); 500 (0.70); 1,000 (0.97); 2,000 (1)
	Symptom-free status **SIAS** (range: 0-1)	79 (-109 to 198)	0.244 (0.14 to 0.34) **	348 (-304 to 1043)	86	14	-	-	0 (0.14); 500 (0.69); 1,000 (0.97); 2,000 (1)
	AQoL QALYs (range: 0-1)	81 (-105 to 200)	0.046 (0.024 to 0.68) **	1945 (-1521 to 6631)	86	14	-	-	0 (0.14); 1,000 (0.32); 2,000 (0.54); 3,000 (0.73); 6,000 (0.96)
Sensitivity Analyses							-	-	
Diagnostic status									
Societal	Diagnostic status (range: 0-1)	-323 (-860 to 64)	0.3 (0.16 to0.43) **	Dominant (to 332)	8	92	-	-	0 (92); 500 (0.99); 1,000 (1)
Healthcare	Diagnostic status (range: 0-1)	79 (-107 to 198)	0.3 (0.16 to0.43) **	288 (-254 to 900)	14	86			0 (0.14); 500 (0.79); 1,000 (0.98)
EQ-5D									
Societal	QALYs (range: 0-1)	-319 (-829 to 63)	-0.00049 (-0.0166 to 0.0174)	112,106[a]	5	48	45	2	0 (0.99); 10,000 (0.89); 100,000 (0.60)
Healthcare	QALYs (range: 0-1)	80 (-100 to 210)	-0.00059 (-0.016 to 0.015)	Dominated[a]	39	9	7	45	0 (0.15); 10,000 (0.26); 100,000 (0.48)

Increased Intervention costs									
+ 50 % intervention costs	QALYs (range: 0-1) (societal)	-230 (-741 to 153)	0.046 (0.024 to 0.68)	Dominant (to 4859)	15	85	-	-	0 (0.84), 1000 (0.89) 2000 (0.92), 3000 (0.95), 10,000 (1)
	QALYs (range: 0-1) (healthcare)	170 (-15 to 289)	0.046 (0.024 to 0.68) **	3995 (325 to 9878)	98	2	-	-	0 (0.02), 1000 (0.06) 2000 (0.16), 3000 (0.34), 10,000 (0.98)
+ 100 % intervention costs	QALYs (range: 0-1) (societal)	-140 (-651 to 242)	0.046 (0.024 to 0.68)	Dominant (to 7417)	28	72	-	-	0 (0.72), 1000 (0.79) 2000 (0.84), 3000 (0.89), 10,000 (99)
	QALYs (range: 0-1) (healthcare)	259 (113 to 404)	0.046 (0.024 to 0.67) **	6045 (2001 to 13346)	100	-	-	-	0 (0.00), 1000 (0.0) 2000 (0.02), 3000 (0.9), 10,000 (0.92)

Costs are expressed in Euros (reference year 2017)

The SUREG model included significant outcome predictors (predictors for costs were age and treatment experience, predictors for outcome effects were baseline variables for each outcome)

[a] The dependably accurate 95% confidence interval for this distribution cannot be defined because there is no line through the origin that excludes alpha/2 of the distribution

[b] The northeast quadrant of the CE plane, indicating that intervention is more effective and more costly

[c] The southeast quadrant of the CE plane, indicating that Intervention is more effective and less costly

[d] The northwest quadrant of the CE plane, indicating that Intervention is less effective and more costly

[e] The southwest quadrant of the CE plane, indicating that Intervention is less effective and less costly

*$p < 0.05$, *CI* confidence interval, *C* costs, *CE-plane* cost-effectiveness plane, *E* effects, *ICER* incremental cost-effectiveness ratio, *SA* sensitivity analysis, *SA1* analyses not including in-patient care, *SA2* analyses adding €±100 to intervention costs, *SA3* analyses for EQ5D QALY, *WTP* willingness to pay

Supplementary Material

Table S1 Unit costs for the type of health service utilized by the participants

Health service type	**Unit**	**Costs (€)**[a]
Physician	Contact	21.53
Orthopedist		26.71
Specialists for internal medicine		66.47
Dermatologist		20.26
Urologist		26.07
ENT specialist		29.09
Neurologist		48.64
Psychotherapist		82.17
Logopedics / speech therapy	Contact	40.56
Physiotherapy		17.30
Ergotherapy / occupational therapy		39.01
Mean remedies		32.29
General hospital / inpatient	Day	648.11
Mental hospital / inpatient		348.26
General hospital / day patient		421.27
Mental hospital / day patient		226.37
Rehabilitation /outpatient	Day	49.43
Rehabilitation /day patient		93.81
Rehabilitation /inpatient		138.19
University counselling center	Contact	48.40
Patient and family costs	**Unit**	**Costs (€)**
Costs for travel[b]	Per kilometer	€0.30 (US$0.40)
Opportunity costs[c]	Per hour	€22.85 (US$30.30)
Informal Care from friends and family[d]	Per hour	€19.63 (US$25.67)

[a] Unit costs were calculated or adjusted by the German consumer price index[89] for the year 2017
[b] Schmidt, L. Einkommenssteuergesetzbuch (EStG) [German Income Tax Code] (2017)
[C] Bock, J.-O. et al. Standardisierte Bewertungssätze aus gesellschaftlicher Perspektive für die gesundheitsökonomische Evaluation. 55 (Nomos Verlagsgesellschaft mbH & Co. KG, 2015)

[d] Bock, J.-O. et al. Ermittlung standardisierter Bewertungssätze aus gesellschaftlicher Perspektive für die gesundheitsökonomische Evaluation. [Calculation of Standardised Unit Costs from a Societal Perspective for Health Economic Evaluation] Das Gesundheitswes. 77, 53–61 (2014)

Table S2 Baseline sample characteristics

Characteristics	All participants ($N = 200$)	IG ($n = 100$)	WLC ($n = 100$)
	N (%)	N (%)	N (%)
Sociodemographic characteristics			
Age (M, SD)	26.70 (6.34)	26.71 (6.08)	26.68 (6.61)
Sex, female	124 (62%)	63 (63%)	61 (61%)
Married or in a relationship	102 (51.0%)	52 (52.0%)	50 (50.0%)
Citizenship			
Germany	150 (75%)	74 (74.0%)	76 (76.0%)
Switzerland	40 (20%)	21 (21.0%)	19 (19.0%)
EEA member	3 (1.5%)	1 (1.0%)	2 (2.0%)
No EEA member	7 (3.5 %)	4 (4.0%)	3 (3.0%)
Study characteristics			
Full-time student	170 (85.0%)	86 (86.0%)	84 (84.0%)
Part-time student	30 (15.0%)	14 (14.0%)	16 (16.0%)
Semester (M, SD)	5.09 (3.38)	4.65 (3.15)	5.53 (3.56)
Work characteristics			
Employed	106 (53.0%)	58 (58.0%)	48 (48.0%)
Full-time employed	17 (8.5%)	9 (9.0%)	8 (8.0%)
Chronic conditions			
Any chronic condition	127 (64%)	66 (66%)	61 (61%)
Treatment utilization			
Previous psychotherapy	68 (34.0%)	38 (38.0%)	30 (30.0%)
Medication at T0	5 (2.5%)	3 (3.0%)	2 (2.0%)

EEA European Economic Area, *M* mean, *SD* standard deviation

Table S3 Treatment response, symptom-free status, and symptom deterioration at 6-month follow-up

	T2[a]				
	IG (n=100)	WLC (n=100)	$\chi 2(1)$	*p*	NNT (95% CI)
Outcome	N (%)	N (%)			
Reliable improvement					
SPS	77	40	28.20	< .001	2.7 (2.0; 4.1)
SIAS	72	28	38.72	< .001	2.3 (1.8; 3.2)
Symptom-free status					
SPS	49	21	17.23	< .001	3.6 (2.5; 6.5)
SIAS	32	11	13.06	< .001	4.8 (3.1; 10.0)
Symptom deterioration					
SPS	3	26	21.33	< .001	-
SIAS	5	29	20.41	< .001	-

[a] Missing data imputed by multiple imputation

CI confidence interval, $\chi 2$ chi square test, *IG* intervention group, *NNT* Number Needed to Treat, *WLC* waitlist control group

3.4 Article 4: Cost-Effectiveness of an iSMI from Employer's Perspective

Authors: Daniel D. Ebert, Fanny Kählke, Claudia Buntrock, Matthias Berking, Filip Smit, Elena Heber, Harald Baumeister, Burkhardt Funk, Helen Riper & Dirk Lehr
Title: A Health Economic Outcome Evaluation of an Internet-Based Mobile-Supported Stress Management Intervention for Employees.
Journal: *Scandinavian Journal of Work, Environment & Health Journal*, Vol. 44, No. 2 (2018) https://www.sjweh.fi/article/3691
DOI: https://doi.org/10.5271/sjweh.3691
Trial register: https://www.drks.de/DRKS00004749

Work-related stress is prevalent among employees and related to sleeping problems and burnout. Meta-analytic evidence shows that stress management is effective when delivered online in short and long-term but evidence on its cost-effectiveness is missing. Thus, this study aimed to evaluate the cost-effectiveness and cost-benefit of a guided internet- and mobile-supported occupational stress-management intervention (iSMI) for employees from the employer's perspective 6 months after randomization. Employees (N = 264) with increased symptoms of perceived stress (Perceived Stress Scale, PSS-10 ≥ 22) were randomly assigned to the iSMI or a waitlist control (WLC) group with unrestricted access to treatment as usual. The iSMI incorporates seven modules (plus one booster) based on Lazarus's transactional model of stress, including problem-solving and emotion-regulation techniques. Participants are supported by an e-coach who provides personalized feedback throughout the intervention. Symptoms of perceived stress and economic data were collected at baseline, and at 6 months following randomization using self-report instruments. A health economic evaluation, including a cost-benefit analysis (CBA) and a cost-effectiveness analysis (CEA) using symptom-free status as primary outcome, was conducted from the employer's perspective. Costs were assessed using the Trimbos Institute and Institute of Medical Technology Questionnaire for Costs Associated with Psychiatric Illness (TiC-P) adapted to the German healthcare system. The intervention costs, including development, hosting, coaching, and value added tax of 19%, were estimated at €299. Statistical uncertainty was assessed using a bootstrapping technique (N = 5000). The intervention generated a net-benefit of €181 (95% confidence interval (CI) [-6043, 1042]) and a benefit-to-cost ratio [BCR (benefit/costs)] of 1.6 (95% CI [-1.2, 4.5]) per participant over 6 months. In addition, the employer gained €0.60 (95% CI [2.2, 3.5]) for every euro invested [(benefits - costs)/(costs × 100)]. The CEA yielded 67% and 98% probabilities, respectively, of being cost-effective at a WTP ceiling of €0 and €2000 for one additional symptom-free employee compared to WLC. Thus, the iSMI was cost-effective and generated less costs when

compared with WLC within six months after randomization. Using an iSMI as part of an occupational healthcare at a workplace represents good value for money.

The manuscript was submitted in August 2017, accepted in September 2017, and published under the terms of Creative Commons Attribution 4.0 license (manuscript can be reproduced) online in November 2017 and in print in March 2018 in the *Scandinavian Journal of Work, Environment & Health Journal (Scand J Work Environ Health*). This is an international open access journal that aims to promote high quality and impactful research in the field of occupational and environmental health and safety.

Contribution: Fanny Kählke is the second author of this published article. Matthias Berking obtained funding for this trial. David D. Ebert and Elena Heber developed the idea of the study including the study design of the efficacy trial. Fanny Kählke chose the methods to conduct a health economic evaluation, cleaned and analyzed the cost-effectiveness data of the study. She wrote the methods and result section supervised by David D. Ebert. All co-authors read, critically revised, and finally approved the published article.

Original article

Scand J Work Environ Health Online-first -article

doi:10.5271/sjweh.3691

A health economic outcome evaluation of an internet-based mobile-supported stress management intervention for employees

by Ebert DD, Kählke F, Buntrock C, Berking M, Smit F, Heber E, Baumeister H, Funk B, Riper H, Lehr D

Occupational internet-based stress management interventions (iSMI) have shown to be effective, but evidence for cost-effectiveness is scarce. We provide evidence for the cost-effectiveness of a guided iSMI from the employer's perspective and show a high probability that this intervention is associated with cost savings due to less absenteeism and greater productivity at work. Offering iSMI represents good value for money in occupational healthcare.

Affiliation: Friedrich-Alexander University Erlangen-Nuremberg, Department of Clinical Psychology and Psychotherapy, Nägelsbachstrasse 25a, Erlangen, 91052, Germany. david.ebert@fau.de

Refers to the following texts of the Journal: 2016;42(5):355-453 2015;41(2):107-218 2014;40(6):539-654 2006;32(1):1-88

Key terms: CBT; cost-benefit analysis; cost-effectiveness analysis; e-health; economic evaluation; evaluation; internet-based intervention; m-health; randomized controlled trial; RCT; stress; stress management; stress management intervention

Additional material

Please note that there is additional material available belonging to this article on the *Scandinavian Journal of Work, Environment & Health* -website.

(13) in clinical populations, such as depression (14–17), anxiety (18), and risky alcohol use (19) as well as in the field of prevention of mental disorders (20–23). Recently a number of trials showed that internet- and mobile-based interventions can be a valuable addition in occupational health including the treatment of insomnia among employees with work-related rumination (12, 24, 25), improving work-related stress (26–33) and the prevention and treatment of depression in workers (11, 34, 35). However, one trial revealed no significant results of internet-based interventions on depression in employees (36–38).

Whereas the efficacy of both face-to-face as well as internet-based approaches for managing work-related stress is well-documented, high quality data on whether such approaches provide good value for money is scarce. The most recent systematic review on economic analyses of occupational health programs was not able to identify any economic evaluation based on a randomized controlled design that focused on stress-management among workers (39).

As resources are restricted, however, employers are not just interested in the effectiveness of such an intervention, but also in the return-on-investment (ROI) (40). However, various intervention outcomes (ie, treatment response) cannot be easily monetarized and cannot thus be included in ROI analyses. Therefore, cost-effectiveness analyses (CEA) that compare the incremental costs and effects of the intervention and the comparator are also important (41).

Hence, the aim of the present study is to evaluate the cost-effectiveness and net-benefits of an internet-based SMI (iSMI) compared to a waitlist control (WLC) condition with unrestricted access to treatment as usual among employees with heightened levels of perceived stress. Analyses in the present study are conducted from the employer's perspective focusing on costs and savings that are relevant to the employer (ie, productivity losses).

Method

Design

A two-armed RCT was conducted to compare a guided iSMI (GET.ON Stress) with a WLC. Both conditions had full access to treatment as usual. Assessments took place at baseline (T1), post-treatment (7 weeks, T2), and 6-month follow-up. Participants were primarily recruited via the occupational health program of a large health insurance company in Germany. Recruitment was directed at the general working population and not restricted to members of the healthcare insurance company. It occurred through announcements on the health care insurance company's website, newspaper articles and advertisements in the membership magazine of the insurance company. Moreover, the insurance company's occupational health management workers informed human resource departments of collaborating small- and medium-sized companies about the possibility for their employees to participate in the trial.

The present health economic evaluation followed guidelines from the ISPOR RCT-CEA Task Force Report and the recommendations of the Consolidated Health Economic Evaluation Reporting Standard (CHEERS) (42, 43). The ISPOR RCT-CEA Task Force report addresses issues related to trial design, selecting data elements, database design and management, analysis, and reporting of results. The aim of the CHEERS statement is to provide recommendations, in the form of a checklist, to optimize reporting of health-economic evaluations. A more detailed description of the study's design can be found in the study protocol (29). In brief, this study was designed as a health-economic evaluation of an occupational stress-management intervention in employees alongside a randomized controlled trial from the employer's perspective.

The sample consisted of 264 employees in Germany, who were randomly allocated with a ratio of 1:1 to the intervention (iSMI) or WLC group. An independent statistician performed the randomization with a web-based program (RandList). Both groups had full access to treatment as usual. Online-assessments took place at baseline (T1), post-treatment (seven weeks, T2), and 6-month follow up (T3).

Participants were primarily recruited via the occupational health program of a large health insurance company in Germany. Recruitment was directed at the general working population and not restricted to those who were insured by the healthcare insurance company. Recruitment was facilitated by announcements on the healthcare insurance company's website, newspaper articles and advertisements in the membership magazine of the insurance company. Moreover, the insurance company's occupational health management workers informed human resource departments of collaborating small- and medium-sized companies about the possibility for their employees to participate in the trial.

Participants were included in the study if they were 18 years or older, currently employed and scored ≥22 on the perceived stress scale (PSS-10). A cut-off value of one standard deviation above the mean PSS-10 of 15.3 [standard deviation (SD 6.2] in a large working population (44) was chosen. The exclusion criteria were suicide risk, and presence of dissociative and / or psychotic symptoms. The Ethics Committee of the Philipps-University of Marburg, Germany, approved the study. The trial was registered (DRKS00004749) in the German clinical trial registry.

Intervention

The iSMI (called "GET.ON Stress") consisted of seven sessions and one booster session four weeks after training completion. The primary aim of this intervention was to reduce stress levels in employees. GET.ON Stress is based on Lazarus' transactional model of stress (45) (for a detailed description of the intervention see (29, 46). It consists of two main components: problem solving and emotion regulation. Problem solving is an evidence-based method that has been proven to be successful in improving mental health (47). On the other hand, employees are also frequently faced with situations that require dealing with unsolvable problems; such situations are often associated with strong negative affective reactions and require effective regulation strategies. Numerous studies indicate that deficits in emotion regulation may be a relevant factor for the development and persistence of mental health symptoms (31, 32). Targeting emotion regulation skills has shown to be promising for reducing a broad range of psychopathological symptoms (48) and a mechanism of change in previous studies on GET.ON Stress (32). While problem-focused coping by means of problem-solving techniques is a well-established component of most CBT stress management trainings, the emotion-focused ways of coping could be regarded as the forgotten component. The intervention consists of eight sessions composed of modules for psycho-education (session 1), problem solving (sessions 2–3), emotion regulation (sessions 4–6), planning for the future (session 7) and a booster session (session 8). Additionally, participants are offered 11 modules that are integrated in sessions 2–6 and that can be chosen based on individual need and/or preference. Additional modules are directed at time management, rumination and worrying, psychological detachment from work, sleep hygiene, rhythm and regularity of sleeping habits, nutrition and exercise, organization of breaks during work, and social support (see table 1 for a session overview). Each session can be completed in approximately 45–60 minutes. We advise participants to do at least one and maximun two sessions a week. Consequently, the training lasts about 4–7 weeks (plus a booster session after 4 weeks). Once participants finish a lesson, they need to wait until they receive feedback from the accompanying e-coach to be able to start with the next lesson. Lessons consist of texts, exercises, and testimonials and also include interactive elements such as audio and video clips. Participants are encouraged to keep a daily online stress diary. A strong focus of the intervention lies on transfer tasks (homework assignments) to integrate newly acquired strategies and techniques into daily life. The training is adaptive as the content is tailored to the specific needs of the individual participant by continuously asking participants to choose among various response options. Subsequent content is then tailored to each participant's response. Using responsive web-design, participants can follow the program on the internet, a tablet or mobile phone. An integrated read-aloud function allows participants to follow narrated lessons. If desired, participants received automatic motivational text messages and small exercises on their mobile phones. These messages aim to support participants in transferring the exercises of the training into their daily lives (eg, short relaxation exercises: "Relax your muscles in your hands and arms for 3 seconds now. Follow your breathing and each time you breathe out, relax a little more."). The participants had the opportunity to choose between "light coach" (one text message every other day) and "intensive coach" (2–3 text messages every day) options. Participants were supported by an e-coach holding a degree in psychology who followed a standardized manual for writing feedback. The e-coaches provided personalized feedback throughout the intervention. Participants completed on average 5.7 sessions (SD 2.32), used the intervention for a mean of 8.27 weeks (SD 8.54, range 0–56), and 93/132 (70.5%) completed all seven sessions. Ten participants (7.6%) did not start the intervention due to lack of time or changes in personal circumstances. Every participant received a maximum of 30 minutes of feedback per session of an e-coach, resulting in a maximum total of 3 hours (rounded) per participant over the whole course.

Outcome measures

Clinical outcome. The primary outcome of the CEA was the number of participants who achieved symptom-free status as measured by the PSS-10 (49). The PSS consists of 10 items rated on a 5-point Likert scale (0=never; 1=almost never; 2=sometimes; 3=fairly often; 4=very often; range 0–40) referring to the past week. Cronbach alphas ranged from 0.70–0.91 over different measurement points in this study (32). The symptom-free status was achieved when participants scored >2 SD below the mean (T1) of the stressed population (25.52, SD 3.91) as according to Jacobson & Truax (30, 50).

Cost outcome. Only costs that were directly relevant for the employer were considered: (i) intervention costs, (ii) costs, due to absenteeism, and (iii) costs due to presentism. Data on productivity losses (absenteeism and presenteeism) due to health problems were assessed at baseline and 6-month follow-up using the relevant module of the "Trimbos Institute and Institute of Medical Technology Questionnaire for Costs Associated with Psychiatric Illness" (TiC-P) adapted to the German context (51). The TiC-P is a self-report questionnaire with a 3-month recall period in the current study. It is a widely used (24, 29, 32, 33, 52) instrument for collecting data on healthcare utilization and productivity losses in patients with mild-to-moderate mental health conditions

(53). The TiC-P has shown a good test–retest reliability indicated by a satisfactory Cohen's kappa for most items related to healthcare consumption and items absent from work as well as presenteeism (54). Cumulated costs over the six months of the trial were estimated using the area under curve (AUC) method to linearly interpolate 3-month costs as measured at each measurement point to cover the full follow-up period of six months (54).

$$AUC = \left(\frac{\frac{Costs\ Baseline}{3} + \frac{Costs\ 6\ months}{3}}{2} \right) * 3 + Costs\ 6\ months$$

All costs were calculated in euros (€) and indexed for the reference year 2013 (index factor 1.04) based on the German consumer price index (55).

Absenteeism

In order to measure absenteeism, participants reported how many days they had been absent from work during the previous three months (lost work days). Absenteeism cost were calculated by applying the human capital approach (53). In doing so, the number of lost work days was multiplied by the participant's average gross daily wage based on their reported monthly salary.

Presenteeism

Presenteeism occurs when people feel ill and therefore are less efficient during work. In order to quantify the costs due to presenteeism, the participants reported both the number of days that they felt ill but continued to work and their personal inefficiency score on a scale from 0–10, where 0 reflects total inefficiency and 10 reflects that they were as efficient as when in good health. Lost work days due to presenteeism were computed by multiplying the number of work days with reduced functioning by the corresponding inefficiency score. This method is called the Osterhaus method (56). Subsequently, based on self-reported monthly salary, their gross wages per hour were calculated and used to calculate the costs that occurred due to presenteeism.

Costs of the intervention

The provider of GET.ON Stress estimated the average price of the intervention to be €299 per participant. This flat tariff contains all costs for developing, providing, website hosting and maintenance, as well as guidance and 19% VAT. Opportunity costs were not included since we assumed that participants would want to use the intervention at home and not at work.

Statistical analysis

This heath economic evaluation was conducted alongside a randomized trial powered to detect a mean standardized difference of d=0.35 in the primary outcome (PSS-10) between the groups at post-measurement. However, it is worth noting that cost data usually have a large variance, which would require very large samples to test economic hypotheses. Such large samples are most likely prohibitive from a financial, logistical and medical-ethics point of view. Therefore, the study was not powered to statistically test differences in economic outcomes. Instead, a probabilistic decision-making approach for making health-economic inferences was used (57). This procedure takes the uncertainty about key parameters (in costs and effects) into account (58, 59) and informs decision-makers on probabilities rather than statistical significance. Perfect information is only available in very few decision-making situations. Probabilities account for the amount of risk each decision carries.

All analyses were conducted in accordance with the intention-to-treat (ITT) principle. All 264 participants completed the PSS and the cost measures at baseline. The missing data was assumed to be missing completely at random as indicated by the Little's overall test of randomness. Missing cost data at T3 (wage, weekly working hours, presenteeism days, absenteeism days) were imputed using the regression imputation procedure in Stata version 13 to obtain predicted values of missing data. Predictors of outcome and dropout were identified by (logistic) regression. Baseline costs of presenteeism and absenteeism, wage, working hours as well as demographic variables, including age, and gender were found to be significant predictors for both categories and were thus included as predictors in the imputation model.

Cost–benefit analysis (CBA)

This study proceeds on the assumption that the employer is the one who pays for the intervention and benefits from cost savings due to decreased presenteeism and absenteeism. Benefits were defined as the difference in total monetarized outcome measures (ie, absenteeism and presenteeism) between study conditions. Positive benefits point to reduced spending. Costs were defined as the intervention costs, which are assumed to be paid by the employer for each employee (estimated at €299). This amount represents the current market price for the complete intervention, which includes access to seven modules + one booster session for 12 months, one individual written feedback per completed lesson and replies to individual questions from the participant on demand until completion of the booster session.

In the present study, the following metrics for costs and benefits are reported: (i) the net benefits (NB =

benefits - costs), the money saved after cost deduction; (ii) the benefit-to-cost ratio (BCR = benefit/cost) to measure the benefits against the costs; and (iii) the return-on-investment (ROI=NB/costs), the amount in euro returned per one euro invested (40, 60).

Statistical uncertainty is taken into account by bootstrapped 95% confidence intervals (95% CI) which are estimated around these measures with 5000 replications using the bias-corrected and accelerated bootstrap procedure as implemented in Stata version 13 (40, 61). Cost savings are indicated when following criteria are met: NB>0, BCR>1, and ROI>1 (40, 62).

Cost-effectiveness analysis

For the CEA, costs and cost offsets (presenteeism + absenteeism + intervention costs) and effects (number of participants with symptom-free status) were calculated for the 6-month period. Subsequently, costs and outcomes were combined into the incremental cost-effectiveness ratio (ICER) using the following formula:

$$ICER = \frac{Cost\ iSMI - Cost\ WLC}{Effect\ iSMI - Effect\ WLC}$$

Since cost data tend to be skewed to the right (58), we used non-parametric bias-corrected accelerated bootstrapping resampling techniques (with 5000 replications) to assess uncertainties surrounding the ICER. The bootstrap analyses were undertaken in the context of Stata's procedure for seemingly unrelated regression equations (SURE) to simultaneously assess incremental costs and incremental effects. The generated ICER were plotted in a cost-effectiveness plane. On the plane, incremental effects between intervention group (IG) and control group (CG) are depicted on the x-axis and the incremental costs between IG and CG are depicted on the y-axis.

If the majority of simulated ICER fall in the south-east quadrant, the intervention is considered to "dominate" the active control groups because better effects are obtained for lower costs. In contrast, in the north-west quadrant the intervention is considered "inferior" to the control group since it is associated with higher costs and worse health outcomes and therefore not considered to be cost-effective (41). ICER in the south-west quadrant point to an intervention being less effective but also less costly than the control condition. Finally, ICER in the north-east quadrant reflect an intervention being more effective and more costly than control condition. In this case, the amount of money a decision-maker is willing to pay for one additional positive outcome is crucial for a new intervention to be adopted or not. The probability that the intervention is cost-effective compared to CG at various willingness-to-pay (WTP) ceilings for one treatment response gained can be shown by the means of the cost-effectiveness acceptability curve (63).

Sensitivity analysis

The robustness of the findings was assessed by performing sensitivity analyses over a range of intervention costs. In the main analysis, we used intervention costs of €299. However, there is uncertainty concerning these costs, as intervention costs may differ once implemented into occupational routine care, for example due to changing demand, supply in the health sector, and preferences of employer and employees. Therefore, two additional sensitivity analyses were conducted assuming higher and lower intervention costs (with ± €100).

Results

Sample

Table 1 presents the baseline characteristics; a comprehensive description can be found in the paper describing the primary efficacy results (30).

Study drop-outs

The study attrition rate was low: 10.6% (28/264) of participants did not complete the 6-month follow-up questionnaires [N=17/132 (12.8%) for the iSMI and N=11/132 (8.33%) in the WLC; χ^2=1.16; P>0.05]. Persons who dropped out did not differ in a meaningful way from those who provided data, neither on baseline stress scores nor any other baseline outcomes, with the exception of worrying (P<0.05).

Clinical outcome

The effect outcome for the CEA was symptom-free status defined at <17.70 on the PSS-10. Therefore, at T3 79/132 (59.8%) in the iSMI were significantly more participants classified as symptom-free compared to 31/132 (23.5%) in the WLC [NNT (number needed to treat)=2.73; χ^2=15.0; P<0.001]. On average, the iSMI improved by 9.75 (SD 6) PSS scores between pre- and 6-month follow-up whereas the WLC improved by 3.0 (SD 6) PSS scores. The analysis of covariance (ANCOVA) confirmed lower scores on the PSS-10 (relative to the WLC) were found in the iSMI group at T3 [$F_{1,261}$=80.17, P<0.001, with large between-group effect sizes (d=1.02; 95% CI 0.76–1.27)] (50).

Table 1. Demographic characteristics. [SD=standard deviations; iSMI=internet/mobile-supported stress management intervention; %=percentages at baseline; WLC=waitlist control; PSS=perceived stress scale.]

Characteristics	All (N=264)				iSMI (N=132)				WLC (N=132)			
	N	%	Mean	SD	N	%	Mean	SD	N	%	Mean	SD
Age			43.3	10.2			42.4	10.7			44.2	9.6
Gender (female),	193	73.1			97	73.5			96	72.7		
Married/partnership	160	60.6			80	60.6			80	60.6		
Experience												
Experience with health trainings	34	12.9			17	12.9			17	12.9		
Previous psychotherapy	95	36.0			52	39.4			43	32.6		
Current psychotherapy	16	6.1			5	3.8			11	8.3		
Work characteristics												
Years of work experience			18.1	11.1			17.2	10.8			18.9	11.2
Full-time employed	204	77.3			105	79.5			99	75.0		
Part-time employed	57	21.6			25	18.9			32	24.2		
On sick leave	3	1.1			2	1.5			1	0.8		
Effect and costs												
PSS-10			25.5	3.9			25.9	4			25.2	4
Presenteeism (euros)			1185	1455			1136	1363			1234	1545
Presenteeism (days)			16.6	16			16.0	14.9			17.3	17
Absenteeism (euros)			814	1756			837	1634			790	1876
Absenteeism (days)			4.7	9			5	8.7			4.4	9.3

Costs outcome

Table 2 shows mean presenteeism and absenteeism days, and similarly hourly wage for the 6-month follow-up assessment. In addition, cumulated costs for the intervention, presenteeism, and absenteeism as well as total cost per group and between-group cost differences are reported. Presenteeism cost (iSMI: €1346; WLC: €1655) caused slightly lower costs compared to absenteeism cost (iSMI: €1578.2; WLC: €1756.6) in both groups. The mean difference in indirect costs (iSMI–WLC) at the 6-month follow-up was €488 per person favoring the intervention group. In the intervention group (iSMI), each participant produced costs of €299 (intervention costs) and therefore saved €189 (SD 434) on average compared to the control group (WLC) in the first six months.

Table 2. Hourly wage, absenteeism, presenteeism, and related costs categorized by condition at 6-month follow-up. [IG=intervention group; CG=control group, WLC=waitlist control, iSMI=internet-based stress-management intervention; SD=standard deviation.]

	IG (iSMI) (N=132)		CG (WLC) (N=132)			
	Mean	SD	Mean	SD	Mean	SD
Hourly wage (euros) [a]	21.54	6.7	21.68	7.9		
Absenteeism days [b, a]	3.64	6.7	5.23	12.2		
Presenteeism days [b, a]	11.32	12.9	11.47	11.9		
Indirect costs (euros) [c]						
Absenteeism (euros) [a]	1578.18	1471	1756.35	1848		
Presenteeism (euros) [a]	1345.79	2184	1655.16	3436		
Intervention costs (euros)	299					
Total costs (euros)	3223	2787	3412	4133	-189	434

[a] Missing data imputed by multiple imputation.
[b] Regarding the last 3 months.
[c] Cumulative costs for each participant during the 6-month follow-up period calculated by the area under the curve (AUC) of linearly interpolated 1-month costs.

Cost benefit analyses (CBA)

The results of the conducted CBA and sensitivity analyses are reported in table 3. Calculations, based on the intervention costs at €299 and costs per person of €3412 in the WLC and €3180 in the iSMI, yielded a net benefit of €181 and a benefit-to-cost ratio [BCR (benefit/costs)] of 1.6 (95% CI -1.2–4.5) after 6 months. Moreover, the [(benefits - costs)/(costs × 100)] was 0.6 (95% CI 2.2–3.5) meaning the employer gains €0.60 for every euro invested within the time span of six months.

Cost-effectiveness analyses (CEA)

Table 4 reports the results of the CEA. ICER $(C_1 - C_0)/(E_1 - E_0)$ is defined as the incremental difference of mean costs between two groups (CG - IG) divided by the incremental difference in positive effects, ie, the amount of symptom-free persons. The IG produced less indirect costs compared to the CG (€3223 versus €3412). Hence, the ICER formula (322 - 3412)/(0.6 - 0.2) yields an adjusted point estimate of -€-521 (95% CI -3123–1900). The negative ICER falls in the south-east quadrant is therefore dominant.

Figure 1 shows the cost-effectiveness plane in which each dot (N=5000) represents one of 5000 bootstrapped replicated ICER. The bulk of ICER fall in the south-east quadrant, indicating that there is a 67% probability that the iSMI generates greater health effects at lower costs compared to the WLC.

Supplementary figure 2 (www.sjweh.fi/show_

Table 3. Results of the main and sensitivity analyses (based on 5000 bootstrap simulations) with N=132 per group. [CI=95% confidence interval, SA=sensitivity analyses; NB=net benefit; BCR=benefit cost ratio; ROI=return on investment]

Analysis	Costs	Benefits	Financial return					
	Total (euros)	Total (euros)	NB [a]	95% CI	BCR [b]	95% CI	ROI [c]	95% CI
Main analyses	299	488	181	-643–1042	1.6	-1.2–4.5	0.61	-2.2–3.5
SA1 (-100 euros)	199	488	281	-543–1142	2.4	-1.7–6.7	1.4	-2.8–5.7
SA2(+100 euros)	399	488	81	-743–942	1.2	-0.8–3.4	0.2	-1.9–2.4

[a] Indicating amount of money (euros) gained after costs are recovered.
[b] Indicating the amount of money (euros) the employer gains for every euro invested.
[c] Indicating the percent of profit per euro invested.

Table 4. Cost-effectiveness analyses based on 5000 replicates of the incremental cost-effectiveness ratio (mean differences in costs from the employer's perspective and in symptom-free status). [CI=confidence interval, SA=sensitivity analysis IG=intervention group, CG=control group, ΔC= incremental costs, ΔE= incremental effects, ICER= incremental cost–effectiveness ratio, NE= eorth-east quadrant, SE=south-east quadrant, SW=south-west quadrant, NW=north-west quadrant]

Analysis	Sample size		Outcome (symptom-free status)	ΔC (euros)	ΔE (symptom-free status)	Euros/symptom-free status		Distribution cost effectiveness plane (%)			
	IG	CG				ICER	95% CI	NE	SE	SW	NW
Main analyses	132	132	PSS-10 <17.70	-188	0.36	-521	-3123–1900	33	67	0.0	0.0
SA1 (-100 euros)	132	132	PSS-10 <17.70	-328	0.36	-804	-3416–1601	25	75	0.0	0.0
SA2 (+100 euros)	132	132	PSS-10 <17.70	-88	0.36	-238	-2836–2206	42	58	0.0	0.0

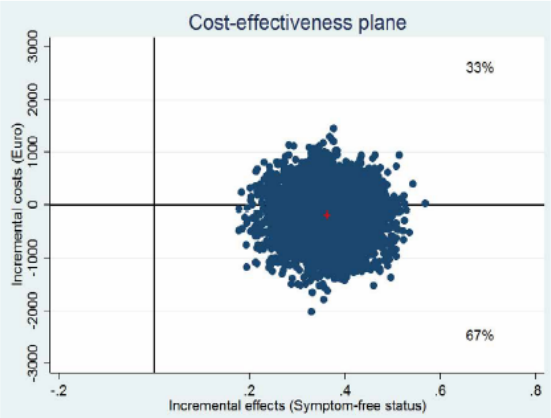


Figure 1. Scatter plot showing the mean differences in costs and effect outcome (symptom-free status) data using 5000 bootstrap replications.

abstract.php?abstract_id=3691) presents the cost-effectiveness acceptability curve, which helps decision-makers decide if the intervention provides "good" value for money given varying willingness-to-pay thresholds. If the employer is willing to pay zero, respectively €500, €1000, €2000 for one additional symptom-free person, there is an 80%, 90% and 98% probability that the IG is more cost-effective than the WLC.

Sensitivity analyses

Both tables 3 and 4 demonstrate results based on the sensitivity analyses. The ICER increased up to -€804 when assuming lower treatment costs (SA1) and the net-benefit rose to €281. When assuming higher intervention costs (SA2), the ICER drops to -€238 but the intervention still has a 58% probability of gaining greater health effects at lower costs compared to the control condition.

Discussion

Main results

The present study took the employer's perspective to evaluate the health economic impacts of an internet-based mobile-supported SMI. Both CEA and CBA indicated that providing the intervention to employees with elevated symptoms of stress is likely to present good value for money in occupational healthcare. The CEA demonstrated a 67% likelihood that the intervention was more cost-effective than no immediate intervention. Likewise, our CBA indicated net-savings of €181 on average per participant already in the first six months following the intervention, with a return on investment of €0.61 per euro invested in the intervention. These savings are mostly due to reductions in absenteeism and presenteeism costs. The estimates can be seen as conservative, as costs due to absenteeism and presenteeism were calculated based on the employee's gross wage only. Costs that occur as a consequence of absenteeism and presenteeism such as reduced productivity and loss in earnings for the employer due to presenteeism and absenteeism were not taken into account. Sensitivity

analyses confirmed the robustness of the findings. If the employer is only willing to pay nothing or €500 for an additional symptom-free person, then there is a 67% and 82%, respectively, probability that the intervention is deemed more cost-effective compared to no immediate intervention.

Comparison with previous findings

This study is, to the best of our knowledge, the first to investigate the cost-effectiveness of a SMI from the employer's perspective. Our results compare favorably to the average ROI [-0.91 versus -0.22 (SD 2.41)] found in 12 RCT in the latest review (39) on the costs and benefits of health promotion at the workplace. The CEA are in line with a recent study on an internet-based intervention targeting insomnia in workers that found a net-benefit of €418 (95% CI -593.03–1488.70) per participant and an ROI of 208% (95% CI -296.52–744.35) (64). Interestingly, the reduction in costs in both studies was mainly driven by the effects of the intervention on presenteeism and to a lesser degree by reduced absenteeism. These findings emphasize the importance of taking indirect cost due to presenteeism into account when investigating health economic effects of interventions in the work-setting. However, our follow-up period was limited to six months only. As chronic stress is associated especially with poor economic consequences in the long run, longer follow-up periods may help to shed light on the true potential and cost savings of the intervention. Such an assumption is supported by one of the few modelling studies that modelled the potential cost-benefit of implementing mental health care interventions in the workplace. They found a net benefit of US$30 per participating worker in year 1 and US$257 in year two following the treatment (65). However, future studies are needed to determine the long-term economic impact of occupational mental health interventions.

Limitations

Limitations of our study include the fact that our large-scale trial was still underpowered for economic analyses. This is a common problem in health-economic evaluations conducted alongside a clinical trial, as cost variables often have a higher variance and generally require greater sample sizes than clinical evaluations (59). Like most randomized trials, the present study was only powered to detect findings on the primary clinical outcome, and in such cases a probabilistic decision-making approach is usually used (58, 59). However, once more studies focusing on a similar target are published, pooling techniques such as individual participant data meta-analyses may be used to overcome this power problem (66–68). Second, only severely distressed participants with high baseline scores (PSS >22) were included in the study. Hence, the results may not apply to populations with lower stress levels and future studies should explore the cost-effectiveness probability for employees with lower stress-levels. Third, self-selection of the participants restrict the generalizability of results to employees willing to utilize such an intervention, with females being more likely to participate. Future studies should focus on reaching men for occupational SMI. Fourth, the assessment of costs due to absenteeism and presenteeism was based on self-reported data. Although this procedure has exhibit reasonably good reliability and validity (53, 69–71) and is standard procedure in health economic outcome evaluations alongside RCT (72), subjective data are prone to certain biases and hence the total costs in both groups may be either an overestimation or underestimation of true overall costs. Fifths, other work-related costs such as staff turnover, early retirement, and somewhat intangible costs such as the firm's reputation as a bad/good place to work were not included and could lead to greater cost-savings. Moreover, we used wages as a basis for measuring productivity costs, which might be a good proxy for true productivity costs only under certain conditions, as the method used ignores, for example, cases in which additional efforts of co-workers compensate productivity lost due to absenteeism and presenteeism of colleagues. Sixth, a WLC design with access to treatment as usual has been chosen where treatment as usual without delayed access is regarded as favorable control conditions (73). Finally, the present evaluation focused solely on costs relevant for the employer and excluded other costs that are relevant for the society, such as direct medical costs. Although indirect costs are often the major cost driver in stress-related health problems accounting for 50–80% of all associated costs (6, 7), future studies should also evaluate the cost-effectiveness from other perspectives, such as the societal or healthcare perspective.

Concluding remarks

There is substantial evidence for the effectiveness of psychological interventions for improving mental and work-related outcomes. However, methodological sound studies on the health economic effects of such interventions are still limited. The present study is the first showing that investing in internet-based stress-management interventions is associated with a high probability for a positive financial return, even when only focusing on costs that are relevant for the employer. In conclusion, when future studies could replicate the current findings, investing in digital interventions aiming to improve mental health at the workplace may be beneficial for employers as seen from a corporate health-economic and business point of view.

Acknowledgements

German healthcare insurance firm BARMER and the European Comission funded this study. The trial is registered with the German Clinical Trials Register (DRKS): DRKS00004749; www.drks.de/drks_web/ (archived by WebCite)

Declaration of interest

DDE, DL, MB and BF are stakeholders of the "Institute for Online Health Trainings", which aims to transfer scientific knowledge related to the present research into routine healthcare.

References

1. Hammen C. Stress and depression. Annu Rev Clin Psychol. 2005 Jan;1:293–319. https://doi.org/10.1146/annurev.clinpsy.1.102803.143938.
2. Richardson S, Shaffer JA, Falzon L, Krupka D, Davidson KW, Edmondson D. Meta-analysis of perceived stress and its association with incident coronary heart disease. Am J Cardiol. 2012 Dec;110(12):1711–6. https://doi.org/10.1016/j.amjcard.2012.08.004.
3. Steptoe A, Kivimäki M. Stress and cardiovascular disease. Nat Rev Cardiol. 2012 Jun;9(6):360–70. https://doi.org/10.1038/nrcardio.2012.45.
4. CIPD (Chartered Institute of Personnel and Development). Building the business case for managing stress in the workplace. London; 2008.
5. Kalia M. Assessing the economic impact of stress--the modern day hidden epidemic. Metabolism. 2002 Jun;51(6 Suppl 1):49–53. https://doi.org/10.1053/meta.2002.33193.
6. Hassard J, Teoh K, Cox T, Dewe P, Cosmar M, Gründler R, et al. Calculating the costs of work-related stress and psychosocial risk - a literatur review. European Agency for Safety and Health at Work. 2014.
7. Uegaki K, Bakker I, de Bruijne M, van der Beek A, Terluin B, van Marwijk H, et al. Cost-effectiveness of a minimal intervention for stress-related sick leave in general practice: results of an economic evaluation alongside a pragmatic randomised control trial. J Affect. 2010;120(1–3):177–87. https://doi.org/10.1016/j.jad.2009.04.012.
8. Rebergen DS, Bruinvels DJ, van Tulder MW, van der Beek AJ, van Mechelen W. Cost-Effectiveness of Guideline-Based Care for Workers with Mental Health Problems. J Occup Environ Med. 2009;51(3):313–22. https://doi.org/10.1097/JOM.0b013e3181990d8e.
9. Richardson KM, Rothstein HR. Effects of occupational stress management intervention programs: a meta-analysis. J Occup Health Psychol. 2008 Jan;13(1):69–93. https://doi.org/10.1037/1076-8998.13.1.69.
10. van der Klink JJ, Blonk RW, Schene AH, van Dijk FJ. The benefits of interventions for work-related stress. Am J Public Health. 2001 Feb;91(2):270–6. https://doi.org/10.2105/AJPH.91.2.270.
11. Junge MN, Lehr D, Bockting CLH, Berking M, Riper H, Cuijpers P, et al. For whom are internet-based Occupational Mental Health Interventions effective? Moderators of internet-based Problem-Solving Training Outcome. internet Interv. Elsevier; 2015;2(1):39–47.
12. Ebert DD, Berking M, Thiart H, Riper H, Laferton J, Lehr D. Restoring depleted resources: Efficacy and mechanisms of change of an internet-based unguided recovery training for better sleep and psychological detachment from work. Heal Psychol. 2015;34S:1240–51. https://doi.org/10.1037/hea0000277.
13. Ebert DD, Daele T, Nordgreen T, Karekla M, Compare TA, Zarbo C, et al. internet and mobile-based psychological interventions: applications, efficacy and potential for improving mental health. A report of the EFPA e-health taskforce. BMJ Open. 2017;7:e016696.
14. Hedman E, Ljótsson B, Lindefors N. Cognitive behavior therapy via the internet: a systematic review of applications, clinical efficacy and cost-effectiveness. Expert Rev Pharmacoecon Outcomes Res. 2012 Dec;12(6):745–64. https://doi.org/10.1586/erp.12.67.
15. Ebert DD, Zarski A-C, Christensen H, Stikkelbroek Y, Cuijpers P, Berking M, et al. internet and computer-based cognitive behavioral therapy for anxiety and depression in youth: a meta-analysis of randomized controlled outcome trials. PLoS One. 2015 Jan;10(3):e0119895. https://doi.org/10.1371/journal.pone.0119895.
16. Ebert DD, Donkin L, Andersson G, Andrews G, Berger T, Carlbring P, et al. Does internet-based guided-self-help for depression cause harm? An individual participant data meta-analysis on deterioration rates and its moderators in randomized controlled trials. Psychol Med. 2016 Sep;46(13):2679–93. https://doi.org/10.1017/S0033291716001562.
17. Königbauer J, Letsch J, Doebler P, Ebert DD, Baumeister H. internet- and Mobile-based Depression Interventions for People with Diagnosed Depression: A Systematic Review and Meta-analysis. J Affect Disord; 2017 Jul;178(0):131–41.
18. Mayo-Wilson E, Montgomery P. Media-delivered cognitive behavioural therapy and behavioural therapy (self-help) for anxiety disorders in adults. Cochrane database Syst Rev. 2013 Jan;9:CD005330. https://doi.org/10.1002/14651858.CD005330.pub4.
19. Riper H, Blankers M, Hadiwijaya H, Cunningham J, Clarke S, Wiers R, et al. Effectiveness of Guided and Unguided Low-Intensity internet Interventions for Adult Alcohol Misuse: A Meta-Analysis. Stewart R, editor. PLoS One. 2014 Jan;9(6):e99912. https://doi.org/10.1371/journal.pone.0099912.
20. Buntrock C, Ebert DD, Lehr D, Smit F, Riper H, Berking M,

et al. Effect of a Web-Based Guided Self-help Intervention for Prevention of Major Depression in Adults With Subthreshold Depression. JAMA. 2016 May 3;315(17):1854–63. https://doi.org/10.1001/jama.2016.4326.

21. Ebert DD, Buntrock C, Cuijpers P, K van Z, P C, C B, et al. Online Intervention for Prevention of Major Depression — Reply. JAMA .2016 Aug;316(8):881. https://doi.org/10.1001/jama.2016.9586.

22. Sander L, Rausch L, Baumeister H. Effectiveness of internet-Based Interventions for the Prevention of Mental Disorders: A Systematic Review and Meta-Analysis. JMIR Ment Health. 2016 Aug 17;3(3):e38. https://doi.org/10.2196/mental.6061.

23. Ebert DD, Cuijpers P, Mu-oz RF, Baumeister H. Prevention of Mental Health Disorders using internet and mobile-based Interventions: a narrative review and recommendations for future research. Front Psychiatry Frontiers; 2017;8:116. https://doi.org/10.3389/fpsyt.2017.00116.

24. Thiart H, Lehr D, Ebert D, Sieland B, Berking M, Riper H. Log in and breathe out: efficacy and cost-effectiveness of an online sleep training for teachers affected by work-related strain - study protocol for a randomized controlled trial. Trials [internet] . Springer Nature; 2013;14(1):169.

25. Thiart H, Lehr D, Ebert DD, Berking M, Riper H. Log in and breathe out: internet-based recovery training for sleepless employees with work-related strain {\textendash} results of a randomized controlled trial. Scand J Work Environ. 2015 Jan;41(2):164–74. https://doi.org/10.5271/sjweh.3478.

26. Ly KH, Asplund K, Andersson G. Stress management for middle managers via an acceptance and commitment-based smartphone application: A randomized controlled trial. internet Interv. 2014 Jul;1(3):95–101. https://doi.org/10.1016/j.invent.2014.06.003.

27. Ruwaard J, Lange A, Bouwman M, Broeksteeg J, Schrieken B. E-mailed standardized cognitive behavioural treatment of work-related stress: a randomized controlled trial. Cogn Behav Ther. 2007 Jan;36(3):179–92. https://doi.org/10.1080/16506070701381863.

28. Aikens KA, Astin J, Pelletier KR, Levanovich K, Baase CM, Park YY, et al. Mindfulness goes to work: impact of an online workplace intervention. J Occup Environ Med. 2014;56(7):721–31. https://doi.org/10.1097/JOM.0000000000000209.

29. Heber E, Ebert DD, Lehr D, Nobis S, Berking M, Riper H. Efficacy and cost-effectiveness of a web-based and mobile stress-management intervention for employees: design of a randomized controlled trial. BMC Public Health . 2013 Jan;13:655. https://doi.org/10.1186/1471-2458-13-655.

30. Heber E, Lehr D, Ebert D, Berking M, Riper H. Web-based and mobile stress management intervention for employees: results of a randomised controlled trial. J Med internet Res. 2016;18(1):e21. https://doi.org/10.2196/jmir.5112.

31. Ebert DD, Lehr D, Smit F, Zarski A-C, Riper H, Heber E, et al. Efficacy and cost-effectiveness of minimal guided and unguided internet-based mobile supported stress-management in employees with occupational stress: a three-armed randomised controlled trial. BMC Public Health . 2014 Aug;14(1):807. https://doi.org/10.1186/1471-2458-14-807.

32. Ebert DD, Lehr D, Heber E, Riper H, Cuijpers P, Berking M. internet- and mobile-based stress management for employees with adherence-focused guidance: efficacy and mechanism of change. Scand J Work Environ Health . 2016 Sep;42(5):382–94. https://doi.org/10.5271/sjweh.3573.

33. Ebert DD, Heber E, Berking M, Riper H, Cuijpers P, Funk B, et al. Self-guided internet-based and mobile-based stress management for employees: Results of a randomised controlled trial. Occup Environ Med. 2016;73(5). https://doi.org/10.1136/oemed-2015-103269.

34. Imamura K, Kawakami N, Furukawa TA, Matsuyama Y, Shimazu A, Umanodan R, et al. Does internet-based cognitive behavioral therapy (iCBT) prevent major depressive episode for workers? A 12-month follow-up of a randomized controlled trial. Psychol Med. 2015 Jul;45(9):1907–17. https://doi.org/10.1017/S0033291714003006.

35. Ebert DD, Lehr D, Boß L, Riper H, Cuijpers P, Andersson G, et al. Efficacy of an internet-based problem-solving training for teachers: Results of a randomized controlled trial. Scand J Work Env Health. 2014;40(6):582–96. https://doi.org/10.5271/sjweh.3449.

36. Geraedts AS, Kleiboer AM, Wiezer NM, Cuijpers P, van Mechelen W, Anema JR. Feasibility of a worker-directed web-based intervention for employees with depressive symptoms. internet Interv. 2014 Jul;1(3):132–40. https://doi.org/10.1016/j.invent.2014.07.001.

37. Geraedts AS, Kleiboer AM, Twisk J, Wiezer NM, van Mechelen W, Cuijpers P. Long-term results of a web-based guided self-help intervention for employees with depressive symptoms: randomized controlled trial. J Med internet Res. 2014 Jan;16(7):e168. https://doi.org/10.2196/jmir.3539.

38. Geraedts AS, Kleiboer AM, Wiezer NM, van Mechelen W, Cuijpers P. Short-term effects of a web-based guided self-help intervention for employees with depressive symptoms: randomized controlled trial. J Med internet Res. 2014 Jan;16(5):e121. https://doi.org/10.2196/jmir.3185.

39. Baxter S, Sanderson K, Venn AJ, Blizzard CL, Palmer AJ. The Relationship Between Return on Investment and Quality of Study Methodology in Workplace Health Promotion Programs. Am J Heal Promot. 2014 Jun;28(6):347–63. https://doi.org/10.4278/ajhp.130731-LIT-395.

40. van Dongen JM, van Wier MF, Tompa E, Bongers PM, van der Beek AJ, van Tulder MW, et al. Trial-Based Economic Evaluations in Occupational Health: Principles, Methods, and Recommendations. J Occup Environ Med. 2014;56(6):563–72. https://doi.org/10.1097/JOM.0000000000000165.

41. Drummond MF, Sculpher MJ, Torrence GW, O'Brien BJ, Stoddart GL. Methods for the Economic Evaluation of health Care Programmes: third ed. Oxford: Oxford University Press; 2005.

42. Husereau D, Drummond M, Petrou S, Carswell C, Moher D, Greenberg D, et al. Consolidated health economic evaluation reporting standards (CHEERS) statement. BMJ. 2013;346. https://doi.org/10.1136/bmj.f1049.

43. Cost-Effectiveness Analysis Alongside Clinical Trials II—An ISPOR Good Research Practices Task Force Report. Value Heal. 2015;18(2):161–72. https://doi.org/10.1016/j.jval.2015.02.001.

44. Lesage F-X, Berjot S, Deschamps F. Psychometric properties of the French versions of the Perceived Stress Scale. Int J Occup Med Environ Health. 2012;25(2):178–84. https://doi.org/10.2478/s13382-012-0024-8.

45. Lazarus RS, Folkman S. Stress, appraisal, and coping [Sutoresuno shinrigaku]. New York, NY: Springer; 1984.

46. Ebert DD, Lehr D, Smit F, Zarski A-C, Riper H, Heber E, et al. Efficacy and cost-effectiveness of minimal guided and unguided internet-based mobile supported stress-management in employees with occupational stress: A three-armed randomised controlled trial. BMC Public Health . 2014;14(1). https://doi.org/10.1186/1471-2458-14-807.

47. Malouff JM, Thorsteinsson EB, Schutte NS. The efficacy of problem solving therapy in reducing mental and physical health problems: a meta-analysis. Clin Psychol Rev. 2007 Jan;27(1):46–57. https://doi.org/10.1016/j.cpr.2005.12.005.

48. Berking M, Ebert DD, Cuijpers P, Hofmann SG. Emotion regulation skills training enhances the efficacy of inpatient cognitive behavioral therapy for major depressive disorder: a randomized controlled trial. Psychother Psychosom. 2013 Jan;82(4):234–45. https://doi.org/10.1159/000348448.

49. Cohen S, Kamarck T, Mermelstein R. A global measure of perceived stress. J Heal Soc Behav. 1983;24. https://doi.org/10.2307/2136404.

50. Jacobson NS, Truax P. Clinical significance: a statistical approach to defining meaningful change in psychotherapy research. J Consult Clin Psychol. 1991 Feb;59(1):12–9. https://doi.org/10.1037/0022-006X.59.1.12.

51. Hakkaart-van Roijen L, Van Straten A, Donker M, Tiemens B. Trimbos/iMTA questionnaire for costs associated with psychiatric illness (TIC-P). Rotterdam Inst Med Technol Assess. 2002.

52. Buntrock C, Berking M, Smit F, Lehr D, Nobis S, Riper H, et al. Preventing Depression in Adults With Subthreshold Depression: Health-Economic Evaluation Alongside a Pragmatic Randomized Controlled Trial of a Web-Based Intervention. J Med internet Res. 2017 Jan;19(1):e5. https://doi.org/10.2196/jmir.6587.

53. Bouwmans C, De Jong K, Timman R, Zijlstra-Vlasveld M, Van der Feltz-Cornelis C, Tan Swan S, et al. Feasibility, reliability and validity of a questionnaire on healthcare consumption and productivity loss in patients with a psychiatric disorder (TiC-P). BMC Health Serv Res. 2013 Jun 15;13:217. https://doi.org/10.1186/1472-6963-13-217.

54. Matthews JN, Altman DG, Campbell MJ, Royston P. Analysis of serial measurements in medical research. BMJ . 1990;300(6719):230–5. https://doi.org/10.1136/bmj.300.6719.230.

55. Destatis. Consumer Price Indices. [internet]. 2015. Available from: https://www.destatis.de/EN/FactsFigures/NationalEconomyEnvironment/.

56. Osterhaus JT, Gutterman DL, Plachetka JR. Healthcare resource and lost labour costs of migraine headache in the US. Pharmacoeconomics. 1992;2(1):67–76. https://doi.org/10.2165/00019053-199202010-00008.

57. van Hout BA, Al MJ, Gordon GS, Rutten FF. Costs, effects and C/E-ratios alongside a clinical trial. Health Econ. 3(5):309–19. https://doi.org/10.1002/hec.4730030505.

58. Briggs AH, Gray AM. Handling uncertainty in economic evaluations of healthcare interventions. BMJ. 1999 Sep;319(7210):635–8. https://doi.org/10.1136/bmj.319.7210.635.

59. Briggs A. Economic evaluation and clinical trials: size matters. BMJ.2000 Dec;321(7273):1362–3. https://doi.org/10.1136/bmj.321.7273.1362.

60. Van Dongen JM, Proper KI, Van Wier MF, Van der Beek AJ, Bongers PM, Van Mechelen W, et al. Systematic review on the financial return of worksite health promotion programmes aimed at improving nutrition and/or increasing physical activity. Obes Rev. 2011;12(12):1031–49. https://doi.org/10.1111/j.1467-789X.2011.00925.x.

61. Dr. Henry AG, Dr. Jalpa AD, Dr. Seema SS, Dr. Daniel P. Designing economic evaluations in clinical trials [internet]. Oxford, UK: "Oxford University Press"; Available from: file://oxfordmedicine.com/10.1093/med/9780199685028.001.0001/med-9780199685028-chapter-2

62. Leigh JP. Expanding research on the economics of occupational health. Scand J Work Environ Health. 2006;32(1):1–4. https://doi.org/10.5271/sjweh.969.

63. Fenwick E, O'Brien B, Briggs A. Cost-effectiveness acceptability curves: facts, fallacies and frequently asked questions. Health Econ. 2004;13. https://doi.org/10.1002/hec.903.

64. Thiart H, Ebert DD, Lehr D, Nobis S, Buntrock C, Berking M, et al. internet-Based Cognitive Behavioral Therapy for Insomnia: A Health Economic Evaluation. Sleep; 2016;39(10):1769–78. https://doi.org/10.5665/sleep.6152.

65. Lo Sasso AT, Rost K, Beck A. Modeling the Impact of Enhanced Depression Treatment on Workplace Functioning and Costs. Med Care . 2006 Apr;44(4):352–8. https://doi.org/10.1097/01.mlr.0000204049.30620.1e.

66. Clarke MJ. Individual patient data meta-analyses. Best Pract Res Clin Obstet Gynaecol. 2005 Feb;19(1):47–55. https://doi.org/10.1016/j.bpobgyn.2004.10.011.

67. Jones AP, Riley RD, Williamson PR, Whitehead A. Meta-analysis of individual patient data versus aggregate data from longitudinal clinical trials. Clin Trials. 2009 Feb;6(1):16–27. https://doi.org/10.1177/1740774508100984.

68. Riley RD, Lambert PC, Abo-Zaid G. Meta-analysis of individual participant data: rationale, conduct, and reporting. BMJ. 2010 Jan;340:c221. https://doi.org/10.1136/bmj.c221.

69. Johns G, Miraglia M. The reliability, validity, and accuracy of self-reported absenteeism from work: A meta-analysis. J Occup Health Psychol. 2015 Jan;20(1):1–14. https://doi.org/10.1037/a0037754.

70. Prasad M, Wahlqvist P, Shikiar R, Shih Y-CT. A Review of Self-Report Instruments Measuring Health-Related Work Productivity. Pharmacoeconomics. 2004;22(4):225–44. https://doi.org/10.2165/00019053-200422040-00002.

71. The Use and Performance of Productivity Scales to Evaluate Presenteeism in Mood Disorders. Value Heal. 2012 Dec;15(8):1148–61. https://doi.org/10.1016/j.jval.2012.08.2206.

72. Lensberg BR, Drummond MF, Danchenko N, Despiégel N, François C. Challenges in measuring and valuing productivity costs, and their relevance in mood disorders. Clinicoecon Outcomes Res. 2013;5:565–73. https://doi.org/10.2147/CEOR.S44866.

73. Furukawa TA, Noma H, Caldwell DM, Honyashiki M, Shinohara K, Imai H, et al. Waiting list may be a nocebo condition in psychotherapy trials: a contribution from network meta-analysis. Acta Psychiatr Scand. 2014 Sep;130(3):181–92. https://doi.org/10.1111/acps.12275.

Received for publication: 1 August 2017

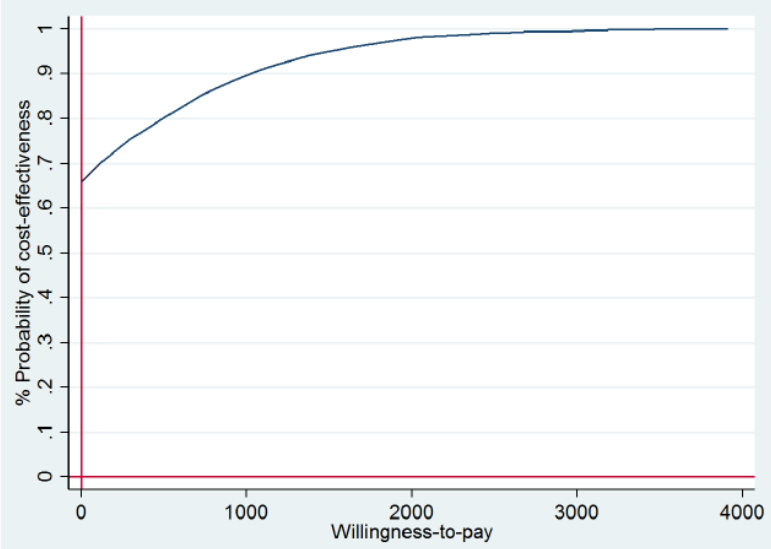
Original article. Scand J Work Environ Health. 2018;44(2):171–182

A health economic outcome evaluation of an internet-based mobile-supported stress management intervention for employees [1]

by David Daniel Ebert, PhD,[2] Fanny Kählke, MA Ed MPH,1 Claudia Buntrock, MSC,1, 2 Matthias Berking, PhD,1, 2 Filip Smit, PhD,3, 4, 5 Elena Heber, PhD,2, 6 Harald Baumeister, PhD,7 Burkhardt Funk, PhD,2
Heleen Riper, PhD,2, 5 Dirk Lehr, PhD 2

1 *Supplementary figure S2*

2 *Correspondence to: David Daniel Ebert, PhD, Friedrich-Alexander University Erlangen-Nuremberg, Department of Clinical Psychology and Psychotherapy, Nägelsbachstrasse 25a, Erlangen, 91052, Germany. [E-mail: david.ebert@fau.de]*



Supplemental Figure S2. Cost-effectiveness acceptability curve (CEAC) for the cost-effectiveness probability depending on varying willingness-to-pay thresholds.

3.5 Article 5: Cost-Effectiveness of an iSMI from Societal Perspective

Authors: Fanny Kählke, Claudia Buntrock, Filip Smit, Matthias Berking, Dirk Lehr, Elena Heber, Burkhardt Funk, Helen Riper & Daniel D. Ebert

Title: Economic Evaluation of an Internet-Based Stress-Management Intervention Alongside a Randomized Controlled Trial

Journal: *JMIR Mental Health,* Vol. 6, No. 5 (2019) https://mental.jmir.org/2019/5/e10866/

DOI: https://doi.org/10.2196/10866

Trial register: https://www.drks.de/DRKS00004749

Work-related stress is widespread among employees and associated with adverse health consequences such as sleeping problems and burnout as well as enormous costs for society. Internet-based stress management interventions (iSMI) are effective in reducing stress at the workplace, but evidence for their cost-effectiveness is lacking. Thus, this study aimed to evaluate the cost-effectiveness of a guided iSMI for employees from the societal perspective 6 months after randomization. Employees (N = 264) with elevated symptoms of perceived stress (Perceived Stress Scale, PSS-10 ≥ 22) were assigned to the iSMI or to a waitlist control (WLC) group with unrestricted access to treatment as usual. The iSMI offers problem-solving and emotion-regulation techniques across seven modules (plus one booster) based on Lazarus' transactional model of stress. The intervention is guided by an e-coach offering personalized feedback for the participants. Symptoms of perceived stress and economic data were collected via self-report instruments at baseline and at six months following randomization. A health economic evaluation, including a cost-utility analysis (CUA) and a cost-effectiveness analysis (CEA), was conducted relating cost to a symptom-free person or quality-adjusted life years (QALYs based on the EQ-5D instrument) from the societal perspective. Costs were assessed using the Trimbos Institute and Institute of Medical Technology Questionnaire for Costs Associated with Psychiatric Illness (TiC-P) adapted to the German healthcare system. The intervention costs, including the development, hosting, coaching, and value added tax were estimated at €299. Statistical uncertainty was assessed using a non-parametric bootstrapping (N = 5000). The iSMI dominated the WLC, generating larger effects at less costs. Thus, at a willingness to pay (WTP) of €0 per additional symptom-free person, the intervention's probability of being more cost-effective than WLC was 70%. This probability rose to 85% and 93% when the society was willing to pay €1000 or €2000, respectively, per additional symptom-free person. Likewise, the CUA yielded a 76% probability that the intervention is more cost-effective than WLC at a WTP threshold of €20,000 (US$25,800) per QALY gained. From a societal perspective, the iSMI shows

an acceptable likelihood of being cost-effective compared with WLC. The integration of this iSMI into routine occupational healthcare can complement the traditional face-to-face therapies provided by occupational health physicians.

The manuscript was submitted in May 2018, accepted in December 2018, and published under the terms of Creative Commons Attribution 4.0 license (manuscript can be reproduced) in May 2019 in the *Journal of Medical Internet Research Mental Health*.

Contribution: Fanny Kählke was the first and main author of the published article. Mathias Berking obtained funding for this trial. David D. Ebert obtained funding for the analysis. Elena Heber was responsible for the study administration. Fanny Kählke analyzed the data and drafted the manuscript on the health economic evaluation supervised by David D. Ebert, Claudia Buntrock and Filip Smit. All co-authors read, critically revised, and finally approved the published article.

Original Paper

Economic Evaluation of an Internet-Based Stress Management Intervention Alongside a Randomized Controlled Trial

Fanny Kählke[1], MPH, MEd; Claudia Buntrock[1], PhD; Filip Smit[2,3,4], PhD; Matthias Berking[1], PhD; Dirk Lehr[5], PhD; Elena Heber[6], PhD; Burkhardt Funk[7], PhD; Heleen Riper[2,8], PhD; David Daniel Ebert[1,2], PhD

[1]Institute for Psychology, Department of Clinical Psychology and Psychotherapy, Friedrich-Alexander-Universität Erlangen-Nürnberg, Erlangen, Germany

[2]Amsterdam Public Health, Department of Clinical, Neuro- and Developmental Psychology, Vrije Universiteit, Amsterdam, Netherlands

[3]Amsterdam Public Health Research Institute, Department of Epidemiology and Biostatistics, VU University Medical Centre, Amsterdam, Netherlands

[4]Netherlands Institute of Public Mental Health, Centre of Health-Economic Evaluation, Trimbos Institute, Utrecht, Netherlands

[5]Institute for Psychology, Department of Health Psychology and Applied Biological Psychology, Leuphana University, Lüneburg, Germany

[6]GET.ON Institute for Online Health Trainings, Hamburg, Germany

[7]Institute of Information Systems, Leuphana University, Lüneburg, Germany

[8]Telepsychiatric Centre, University of Southern Denmark, Odense, Denmark

Corresponding Author:
Fanny Kählke, MPH, MEd
Institute for Psychology
Department of Clinical Psychology and Psychotherapy
Friedrich-Alexander-Universität Erlangen-Nürnberg
2nd Floor
Nägelsbachstrasse 25a
Erlangen, 91052
Germany
Phone: 49 9131 85 ext 67568
Fax: 49 9131 85 67576
Email: fanny.kaehlke@fau.de

Abstract

Background: Work-related stress is widespread among employees and associated with high costs for German society. Internet-based stress management interventions (iSMIs) are effective in reducing such stress. However, evidence for their cost-effectiveness is scant.

Objective: The aim of this study was to assess the cost-effectiveness of a guided iSMI for employees.

Methods: A sample of 264 employees with elevated symptoms of perceived stress (Perceived Stress Scale≥22) was assigned to either the iSMI or a waitlist control condition (WLC) with unrestricted access to treatment as usual. Participants were recruited in Germany in 2013 and followed through 2014, and data were analyzed in 2017. The iSMI consisted of 7 sessions plus 1 booster session. It was based on problem-solving therapy and emotion regulation techniques. Costs were measured from the societal perspective, including all direct and indirect medical costs. We performed a cost-effectiveness analysis and a cost-utility analysis relating costs to a symptom-free person and quality-adjusted life years (QALYs) gained, respectively. Sampling uncertainty was handled using nonparametric bootstrapping (N=5000).

Results: When the society is not willing to pay anything to get an additional symptom-free person (eg, willingness-to-pay [WTP]=€0), there was a 70% probability that the intervention is more cost-effective than WLC. This probability rose to 85% and 93% when the society is willing to pay €1000 and €2000, respectively, for achieving an additional symptom-free person. The cost-utility analysis yielded a 76% probability that the intervention is more cost-effective than WLC at a conservative WTP threshold of €20,000 (US $25,800) per QALY gained.

Conclusions: Offering an iSMI to stressed employees has an acceptable likelihood of being cost-effective compared with WLC.

Trial Registration: German Clinical Trials Register DRKS00004749; https://www.drks.de/DRKS00004749

International Registered Report Identifier (IRRID): RR2-10.1186/1471-2458-13-655

(JMIR Ment Health 2019;6(5):e10866) doi: 10.2196/10866

KEYWORDS

work; occupational stress; economic evaluation; internet; quality of life; clinical trials, randomized

Introduction

Background

Up to 27% of the workforce in Europe suffers from elevated stress levels [1]. According to the effort-reward imbalance model [2] and the job demand-control model [3] situations characterized by an imbalance between high effort (eg, workload) and low reward (eg, job insecurity) or high demand and low job decision latitude lead to high levels of strain. This strain is known to be a risk factor for psychological and physiological health consequences such as sleeping problems [4], mental health problems [5], cardiovascular disease [6], and chronic pain [7]. Consequently, the resulting economic burden due to productivity losses (eg, sick leave) [8] and higher health care consumption and out-of-pocket payments is substantial [9-11]. The estimated costs of work-related stress range from US $221.13 million to US $187 billion and therefore impose a tremendous burden on society [12]. Psychological interventions can be effective in reducing stress [13], but the availability of face-to-face treatments is limited [14]. Web-based and mobile-based interventions have been proposed to overcome the limitations of traditional face-to-face interventions. Such interventions are low-threshold interventions, are available 24/7, and are associated with low costs [15].

In a recent meta-analysis, it has been shown that internet-based stress management interventions (iSMIs) are effective with an effect size of d=0.43 (95% CI 0.31-0.51) on perceived stress [16] and a small effect on depression and anxiety, but lack evidence regarding cost-effectiveness. Internet-based interventions are often argued to be cost-effective, yet there exists little evidence. Donker et al [17] found that internet-based interventions for common mental health disorders have a considerable probability of being more cost-effective when compared with control groups. Most health economic outcome studies evaluated internet-based interventions for alcohol consumption [18], smoking cessation [19], anxiety [20], and depression [17,21]. Hedman et al compared an iSMI with an internet-based cognitive behavior therapy (iCBT) for treatment of health anxiety, where the iSMI resulted in lower costs [22].

Objectives

To our knowledge, there exist no cost-effectiveness and cost-utility analyses of iSMIs from the societal perspective. Thus our aim was to establish the cost-effectiveness and cost-utility of this iSMI for employees.

Methods

Design

This study is a health-economic evaluation with a 6-month time horizon from a societal perspective alongside a 2-arm randomized controlled trial (RCT) in Germany to establish the cost-effectiveness and cost-utility of an iSMI for employees with elevated work-related stress in combination with usual care compared with a waitlist control condition (WLC) with access to treatment as usual [23]. The present health-economic evaluation followed guidelines from the International Society for Pharmacoeconomics and Outcomes Research RCT-cost-effectiveness analysis Task Force report and the recommendations of the Consolidated Health Economic Evaluation Reporting Standard [24,25]. The trial included 264 participants who were randomly allocated in a 1:1 ratio with a block size of 2 to either iSMI or WLC. An independent researcher not otherwise involved in the study performed the randomization using randomization software (Randlist, Datinf GmbH) [26]. Participants were included in the study if they were 18 years or older, currently employed, and scored 22 or above on the Perceived Stress Scale (PSS-10). One SD (SD 6.2) above the mean (PSS-10=15.3) in a large working population [27] was chosen as a cut-off value to select participants with an elevated level of stress. The exclusion criteria were to be at risk of suicide or dissociative symptoms or having been diagnosed with a psychosis. The Ethics Committee of the Philipps-University of Marburg, Germany, approved the study. The trial was registered (DRKS00004749) in the German Clinical Trials Register.

Intervention

The most popular models to explain work-related stress are the effort-reward imbalance and the job demand-control model. According to the effort-reward imbalance model [2], work-related stress is generated by high effort (eg, pace of work and workload) and low reward received in return (eg, inadequate salary, promotion prospects, and job security). The job demand-control model [3] identifies high demand (eg, high workload) and low job decision latitude (eg, autonomy and control over the job) as factors that lead to high levels of job strain. This strain is known to be a risk factor for adverse health consequences, such as mental health problems [5], chronic pain [7], and cardiovascular disease [6]. Ideally, job strain should be reduced by changing adverse working conditions such as small rooms and bad equipment. As changing these may be difficult, stressors on an individual level such as inadequate coping strategies can also be addressed. Interventions based on Lazarus's transactional model aim to empower the individual to reduce or modify problems at work (ie, high effort, low rewards, or low decision latitudes). This model identifies 2 strategies of coping with stressors: problem-oriented coping, to actively change or adapt stressors, and emotion-oriented coping, to cope with negative emotions due to stressors at the workplace. Thus, the iSMI is based on 2 main components: problem solving and emotion regulation. Problem solving is an evidence-based method for dealing with such problems and has been proven to be successful in improving mental health [28]. However, employees are frequently faced with unsolvable problems, which are associated with strong negative affective reactions and require effective regulation strategies. Improvement of emotion

regulation skills has been shown to be both promising for reducing psychopathological symptoms [29] and a mechanism of change in previous studies using this iSMI [30]. Deficits in emotion regulation may also be an important factor for the development and persistence of mental health symptoms [31]. Yet, emotion-focused coping is regarded as the forgotten component, whereas problem-focused coping by means of problem-solving techniques is a well-established component of most cognitive-behavioral stress management trainings.

The iSMI is based on Lazarus's transactional model of stress and includes problem solving and emotion regulation. The intervention consists of 8 sessions composed of modules for psycho-education (session 1), problem solving (sessions 2 and 3), emotion regulation (sessions 4-6), planning for the future (session 7), and a booster session (session 8). In addition, participants could choose optional modules covering different topics, for example, time management, rumination and worrying, psychological detachment from work, and sleep hygiene. Each module takes approximately 45 to 60 min to complete. Participants were advised to complete 1 to 2 modules per week. Transfer tasks such as homework assignments were integrated into the intervention to help participants integrate learned skills into daily life. Participants received nontherapeutic feedback by an e-Coach after each completed module. E-Coaches had a degree in psychology, and feedbacks were based on a standardized manual on feedback writing. Participants could also opt in for an additional text message coach along the iSMI (eg, short relaxation exercises). A detailed description of the iSMI can be found elsewhere [32]. The clinical effectiveness of the iSMI has been positively evaluated in a series of RCTs [23,30,31,33,34].

Outcome Measures

Self-reported measures of stress and social functioning (PSS-10 and Short-Form Six-Dimension; SF-6D) were collected at baseline (T1), post treatment (T2; 7 weeks after randomization), and 6-month follow-up (T3) using a secured Web-based assessment system (AES, 256-bit encrypted).

Clinical Outcome

The level of perceived stress was measured by the PSS-10 [27]. Cronbach alphas indicated that the internal consistency ranged from .70 to .91 over different measurement points in this study [30]. Symptom-free status was operationalized as scoring 2 SDs below the PSS-10 sample mean at T1 (mean 25.52, SD 3.91) [23,35].

Quality-Adjusted Life Years

Quality-Adjusted Life Years (QALYs) were used as the primary outcome in the cost-utility analysis. QALYs were computed using the SF-6D [36]. A QALY gain of 0.5 indicates full health throughout the 6-month trial period. The SF-6D is more sensitive to change in mild conditions than the more commonly used EQ-5D and was used for the main analysis [37].

Resource Use and Costing

We assessed direct and indirect costs which occurred over the previous 3 months at baseline, and at 6-month follow-up. All costs were calculated in Euros for the reference year 2013 (index factor 1.04 based on the year 2010), referring to the German consumer price index [38]. Costs were converted to US dollar using the purchasing power parities reported by the Organization for Economic Cooperation and Development. For the reference year 2013, €1 was equated to US $1.29.

The Trimbos Institute and Institute of Medical Technology Questionnaire for Costs Associated with Psychiatric Illness (TiC-P) adapted to the German health care system was used [39]. This is a widely used and reliable instrument for collecting self-reported data on health care utilization and productivity losses in patients with mild to moderate mental health conditions [40-46]. The German version has been used in a number of health economic evaluations alongside randomized trials [21,41,42,44]. The standard unit cost prices were multiplied by the units of resource use for each participant. Multimedia Appendix 1 presents direct medical and direct nonmedical costs by health service type. Cumulated costs of the trial were estimated using the area under curve method to linearly interpolate 3 months costs as measured at each measurement point to cover the full follow-up period of 6 months [47].

Health Care Costs

Health care costs were calculated according to the guidelines of Kraut and Bock et al [48,49]. We included unit costs for a physician; a medical specialist; psychological services such as a psychiatrist and psychotherapist; and allied health services such as physiotherapy, massage, occupational therapy, as well as inpatient care and rehabilitation.

Medication

Unit costs of prescription drugs were calculated using the German register for pharmaceutical drugs *Rote Liste* [50]. The basis for calculating costs of prescribed medication is the pharmacy retail price accounting for a specific pharmacy and manufacture's discount. The discount rates vary between private and statutory health insurances [48]. Therefore, we weighted the mean costs of the 3 largest packages with the same agent based on the daily defined dose by the statutory population share (88,80% of the German population are statutorily insured).

Intervention Costs

The provider (GET.ON Institute GmbH) of the iSMI intervention GET.ON Stress estimated the current market price of the intervention at €299 (US $386) per participant. This flat tariff covers all costs for developing and hosting the intervention plus coaching of the participants. In general, it was assumed that every participant owned a computer, had access to the internet, and used the iSMI in their leisure time after working hours. Hence, these costs were not included.

Patient and Family Costs

Participants self-reported the cost of their out-of-pocket expenses (eg, for over-the-counter drugs). Direct nonmedical travel costs were calculated based on self-reported data that included the used method of transportation (ie, bus, taxi, or car) and round-trip distance to reach health care services. Each kilometer by car was valued at €0.30 [51]. Time spent by participants completing the intervention and/or receiving or waiting for treatment by a physician was considered part of their leisure

time. The opportunity cost of leisure time, defined as the cost associated with the next best alternative use of a particular resource, was valued at €23.10 per hour. This was based on Bock et al's recommendations [48], which estimated these costs based on the average net wage of German employees plus their average pension and unemployment insurance contributions.

Costs incurred from a domestic help (help with daily chores) or production losses resulting from unpaid work such as informal care by friends and family were calculated using the substitution method. These costs were based on the average gross hourly wage earned by a domestic worker, as suggested by Bock et al [48]. This time was valued at €18.33 per hour.

Costs of Productivity Losses

Absenteeism costs were calculated by applying the human capital approach [52]. In doing so, the number of work loss days was multiplied by the participant's average gross daily wage based on their reported monthly salary. In addition, participants reported the number of workdays for which they reported lesser efficiency. On the basis of the Osterhaus method [53], these days were multiplied by an inefficiency score, which resulted in lost-workday equivalents due to presenteeism. Subsequently, based on self-reported monthly salary, their gross wages per day were calculated and used to calculate the costs that occurred due to presenteeism.

Statistical Analysis

This study was powered to detect a mean difference of d=0.35 in the primary outcome (PSS) between the groups at post measurement. Cost data are usually heavily skewed to the right, with large variance requiring very large sample sizes to test the statistical significance of cost differences. Instead, we adopted a probabilistic decision-making approach for our economic analyses [54]. This procedure takes the stochastic uncertainty of the trial data into account [55] and informs the decision makers on probabilities rather than statistical significance. Due to the 6-month follow-up period, no discounting was applied.

All analyses were conducted in accordance with the intention-to-treat (ITT) principle. Missing clinical outcome data were imputed using a Markov Chain Monte Carlo multivariate imputation algorithm with 10 estimations per missing value.

Missing cost data were imputed using the regression imputation procedure implemented in Stata to obtain the required predicted values. Predictors of outcome and dropout were identified via (logistic) regression. Differences in PSS score and symptom-free status between groups were assessed at follow-up using the Chi-square test. At baseline, mean SF-6D utility values were similar in both groups (WLC: mean 0.65, SD 0.08 and iSMI: mean 0.65, SD 0.11). Therefore, no baseline adjustments were made when calculating QALYs. Differences in QALYs between iSMI and WLC were assessed using independent samples t tests.

Analysis of Cost-Effectiveness and Cost-Utility

For the cost-effectiveness analyses, the incremental cost-effectiveness ratio (ICER) was calculated as incremental costs per unit of effect (QALY and symptom-free status). Symptom-free status is meaningful for decision makers and was used as the preferred effect measure as there was no difference between beta coefficients from an OLS regression on the binary outcome compared with beta coefficients from a linear probability model in GLM (GLM: beta=.36, P<.001 and OLS: beta=.36, P<.001).

The ICER was calculated as ICER=($costs_{iSMI}$−$costs_{WLC}$) /($effects_{iSMI}$−$effects_{WLC}$), where costs are the cumulated *costs* over the 6-month period and *effect* are QALY gains or symptom-free status.

Stochastic uncertainty in the ICER was handled using nonparametric bootstrapping, which is a resampling technique applied to the trial data, which generates 5000 simulations of the ICER. The incremental costs and incremental effects were obtained under a bootstrapped seemingly unrelated regression equations model and allowed for correlated residuals of the cost and effect equations [56]. The 5000 bootstrap replications of costs and effects were also used to obtain 95% CIs based on the percentile method.

In a next step, the simulated ICERs were plotted in a cost-effectiveness plane. On the plane, incremental effects are depicted on the horizontal x-axis and the incremental costs on the vertical y-axis. Each dot in the cost-effectiveness plane represents 1 bootstrapped ICER.

The willingness-to-pay (WTP) threshold reflects the maximum amount the society would be willing to pay for a health benefit (eg, a symptom-free person or a QALY gained). As the WTP ceiling for gaining 1 unit of health (eg, gaining 1 QALY or obtaining symptomatic remission in 1 person) is an unknown quantity, a cost-effectiveness acceptability curve was presented, which displays the probability of the intervention being cost-effective for 1 additional unit of health gained at varying WTP ceilings. All analyses were performed using Stata version 13 [57].

Sensitivity Analyses

The robustness of the outcomes was assessed using several sensitivity analyses. First, we used the EQ-5D-3L (European Quality of Life 5 Dimensions 3 Level) instrument [58] for the calculation of QALYs. Second, there is uncertainty regarding the cost of the intervention due to changing demand. Therefore, we conducted sensitivity analyses assuming higher and lower interventions costs (±€100). Third, inpatient costs tend to be very high, but they were only reported by a few participants (n=9, 3.4%). Such outliers may lead to distorted outcomes results, so they were removed in the final sensitivity analysis.

Results

Sample

Multimedia Appendix 2 presents the baseline characteristics. Interested participants were recruited from the general working population via mass media (eg, newspaper articles and television) and with the aid of a health insurance company (BARMER) within their occupational health management program. An open-access website [59] was used to sign-up for study participation. The sample predominately consisted of full-time employed middle-aged women living with a partner. A comprehensive description of the study sample and the

participant flow can be found elsewhere [23]. We did not observe any clinically relevant baseline differences between study conditions.

Study Dropouts

The study attrition was low: 10.6% (28/264) of participants did not complete the 6-month follow-up assessment. The dropout rates between the groups, with 12.8% (17/132) in the iSMI condition and 8.33% (11/132) in the WLC condition, did not differ significantly (χ^2_1=1.4 P=.23).

Outcome Measures

The iSMI improved by 9.75 (SD 6) PSS-10 stress units between pre and 6-month follow-up, whereas the WLC improved by 3.0 units (SD 6) PSS. Differences regarding symptom-free status based on the PSS-10 between groups were assessed at follow-up (iSMI: 79/132, 59.8%; WLC: 31/132, 23.5%; χ^2_1=35.9; P<.001; NNT (Number needed to treat) =2.75, 95% CI 2.11-3.95) [23]. However, the intervention and the WLC did not differ significantly in terms of SF-6D QALY gains (iSMI=0.35, SD 0.04 vs WLC=0.35, SD 0.35; t_{262}=−1.625; P=.10).

Costs

At baseline, mean total costs were €3239 (US $4178) in the iSMI and €3183 (US $4178) in the WLC, which is only a small difference of €56 (US $72), indicating that randomization had resulted in a well-balanced trial. Table 1 presents the average 6-month accumulated per-participant costs by study condition. The costs are clustered into health care costs, patient and family costs, and costs stemming from productivity losses. After 6 months, total incremental costs were €380 (US $490); thus, the iSMI group had less costs than WLC (iSMI: €5258 and WLC: €5642). Health care costs were, on average, higher in the iSMI group compared with WLC. Hospital admissions were a major cost driver. Regarding the patient and family costs, the iSMI had less costs than WLC. Informal care was decreased by €241 for the iSMI. Finally, productivity losses produced the highest cost differences of €487, exceeding the intervention costs, meaning that the iSMI produced less cost than WLC.

Cost-Effectiveness

Table 2 shows the incremental costs, effects, and cost-effectiveness ratios based on 5000 bootstrapped simulations. The bootstrapped ICER for symptom-free status on the PSS-10 was dominant. The cost-effectiveness plane is shown in Figure 1. The majority (70%) of the bootstrapped ICERs fell in the south-east quadrant, indicating a 70% probability that the intervention produces greater health at lower costs than WLC. Hence, the iSMI intervention dominates the WLC condition from a societal perspective. The remaining 30% of ICERs fell in the north-east quadrant, indicating a 30% probability that the intervention produces greater health at greater costs than WLC. Figure 2 presents the cost-effectiveness acceptability curve. If the decision maker is willing to pay €1000 and €3000 for gaining a symptom-free person, the intervention's probability of being more cost-effective than WLC rises to 85% and 97%, respectively.

Table 1. Average costs per participant (in €) by condition at 6-months follow-up (area under the curve, intention-to-treat-sample, N=264).

Cost category	Internet-based stress management intervention (n=132), mean (SD)	Waitlist control condition (n=132), mean (SD)	Incremental costs, difference
Health care costs (€)			
Intervention	299 (Reflects a fixed price)	0 (Reflects a fixed price)	299
Physician services	132 (139)	147 (175)	−15
Psychological services	111 (291)	209 (468)	−98
Hospital in-patient	342 (2222)	188 (1237)	154
Hospital semiresidential	234 (1444)	77 (798)	157
Rehabilitation	8 (41)	89 (658)	−81
Nonphysician services	167 (293)	174 (314)	−7
Prescription drugs	50 (97)	56 (105)	−6
Patient and family costs (€)			
Over the counter drugs	48 (88)	48 (78)	0
Opportunity costs	485 (754)	526 (892)	−42
Travel expenses	27 (48)	49 (94)	−21
Domestic help or informal care	424 (1213)	665 (1327)	−241
Productivity losses (€)			
Absenteeism	1346 (2184)	1655 (3436)	−309
Presenteeism	1578 (1471)	1756 (1849)	−178
Total costs (€)[a]	5258 (5493)	5642 (6000)	−384

[a]Due to rounding, numbers presented may not add up precisely to the totals provided.

Table 2. Results of the main and sensitivity analysis based on 5000 bootstrap simulations. Costs are expressed in 2013 Euros.

Analysis and outcome	Incremental costs, € (95% CI)	Incremental effects, points (95% CI)	Incremental cost-effectiveness ratio, €/points (95% CI)[a]	Distribution over the cost-effectiveness plane, %			
				North-east quadrant[b]	South-east quadrant[c]	South-west quadrant[d]	North-west quadrant[e]
Main analysis							
Perceived stress (range 0-40)	−386 (−1794 to 1006)	6.27 (4.9 to 7.7)[f]	Dominant (dominant to 171)	30	70	__g	—
Symptom-free status (0/1)	−386 (−1794 to 1006)	0.362 (0.25 to 0.47)[f]	Dominant (dominant to 3360)	30	70	—	—
QALYs[h] (range: 0-1)	−386 (−1794 to 1006)	0.0074 (−0015 to 0.016)	Dominant[i]	26	69	2	3
Sensitivity analysis 1[j]							
Perceived stress (range 0-40)	−616 (−1731 to 485)	6.27 (4.9 to 7.7)[f]	Dominant (dominant to 81)	13	87	—	—
Symptom-free status (0/1)	−616 (−1731 to 485)	0.362 (0.25 to 0.47)[f]	Dominant (dominant to 1415)	13	87	—	—
QALYs (range: 0-1)	−616 (−1731 to 485)	0.0074 (−0015 to 0.016)	Dominant[i]	12	83	2	3
Sensitivity analysis 2[k], €+100 added to intervention costs							
Perceived stress (range 0-40)	−286 (−1694 to 1106)	6.27 (4.9 to 7.7)[f]	Dominant (dominant to 187)	34	66	—	—
Symptom-free status (0/1)	−286 (−1694 to 1106)	0.362 (0.25 to 0.47)[f]	Dominant (dominant to 3419)	34	66	—	—
QALYs (range: 0-1)	−286 (−1694 to 1106)	0.0075 (−0015 to 0.016)	Dominant[i]	31	64	2	3
Sensitivity analysis 2[k], €-100 added to intervention costs							
Perceived stress (range 0-40)	−486 (−1894 to 906)	6.27 (4.9 to 7.7)[f]	Dominant (dominant to 155)	24	76	—	—
Symptom-free status (0/1)	−486 (−1894 to 906)	0.362 (0.25 to 0.47)[f]	Dominant (dominant to 2764)	24	76	—	—
QALYs (range: 0-1)	−486 (−1894 to 906)	0.0075 (−0015 to 0.016)	Dominant[i]	22	73	2	3
Sensitivity analysis 3[l]							
QALYs (range: 0-1)	−386 (−1794 to 1006)	0.00186 (−0.010 to 0.014)	Dominant[i]	49	14	22	16

[a]In line with the best practice ISPOR guidelines on 'Model Parameter Estimation and Uncertainty' we did not report negative incremental cost-effectiveness ratios (ICERs) as they are meaningless. Instead we used the term dominant which implies that the intervention has a higher effect and less cost compared with the WLC.

[b]The north-east quadrant of the CE plane, indicating that intervention is more effective and more costly.

[c]The south-east quadrant of the CE plane, indicating that intervention is more effective and less costly.

[d]The south-west quadrant of the CE plane, indicating that intervention is less effective and less costly.

[e]The north-west quadrant of the CE plane, indicating that intervention is less effective and more costly.

[f]$P<.05$.

[g]The distribution of the ICERs (N=5000) sums to 100%. If the distribution only falls into 2 quadrants, there will not be any ICER in the other 2 quadrants (= 0%).

[h]QALYs: quality-adjusted life years.

[i]A dependably accurate 95% confidence interval for this distribution cannot be defined because there is no line through the origin that excludes alpha/2 of the distribution.

[j]Sensitivity analysis 1 analyses not including in-patient care.

[k]Sensitivity analysis 2 analyses adding €±100 of intervention costs.

[l]Sensitivity analysis 3 analyses for EQ5D quality-adjusted life years.

Figure 1. Scatterplot of 5000 replicates of the incremental cost-effectiveness ratio (mean differences in costs and symptom-free status) on the cost-effectiveness plane: internet-based stress-management intervention versus waitlist control condition.

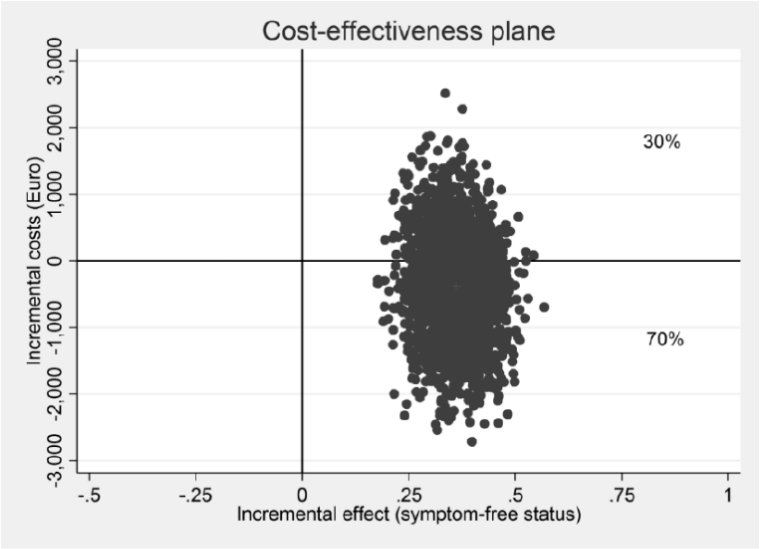
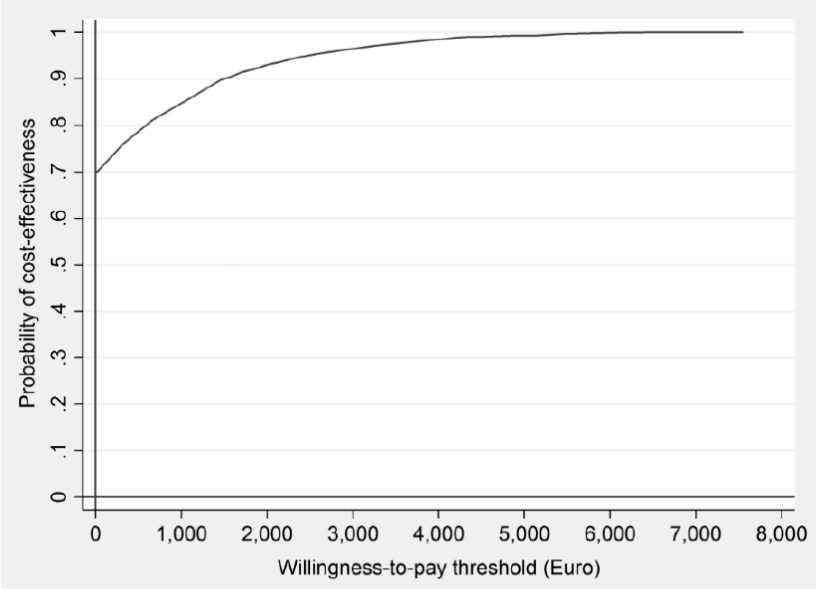


Figure 2. Cost-effectiveness acceptability curve showing the probability of the internet-based stress-management intervention being cost-effective at varying willingness-to-pay ceilings (based on 5000 replicates of the incremental cost-effectiveness ratio using mean differences in costs and symptom-free status).



Cost-Utility

The ICER based on QALY gains showed a small health benefit (approximately 0.001 QALYs gained) for lower mean costs (€386; US $498). Of the simulated ICERs, 69% (as seen in Figure 3) fell in the south-east quadrant, reflecting the intervention's probability of dominating WLC, whereas 26% fell in the north-east quadrant , indicating higher costs and health gains, and 2% fell in the south-west quadrant and 3% in north-west quadrant. Assuming a WTP of €10,000 and €20,000 for gaining 1 QALY, the probability rose to 73% and 76%, respectively (Figure 4).

Figure 3. Scatterplot of 5000 replicates of the incremental cost-effectiveness ratio (mean differences in costs and quality-adjusted life years based on the Short-Form Six-Dimension) on the cost-effectiveness plane: internet-based stress-management intervention versus waitlist control condition. QALY: quality-adjusted life years; SF-6D: Short-Form Six-Dimension.

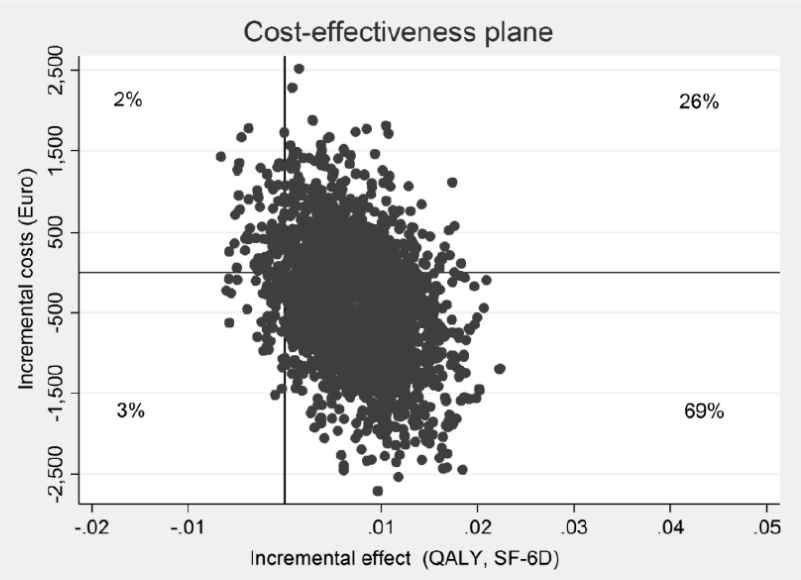
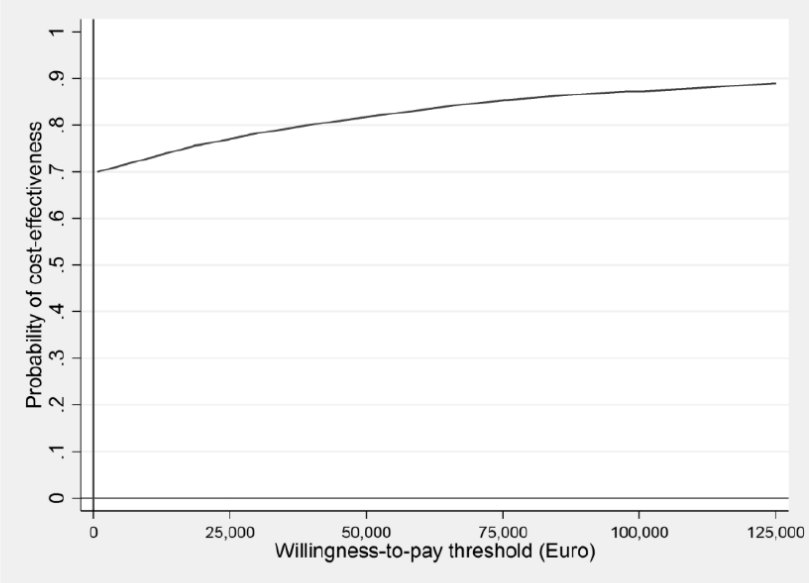


Figure 4. Cost-effectiveness acceptability curve showing the probability of the internet-based stress-management intervention being cost-effective at varying willingness-to-pay ceilings (based on 5000 replicates of the incremental cost-effectiveness ratio using mean differences in costs and quality-adjusted life years based on the Short-Form Six-Dimension). QALY: quality-adjusted life years; SF-6D: Short-Form Six-Dimension.



Sensitivity Analyses

Using the EQ-5D-3L resulted in a smaller incremental QALY gain in favor of the intervention group (0.28 QALY, SD 0.05) compared with WLC (0.28 QALY, SD 0.05), which was not statistically significant (t_{262}=−0.296; P=.77). This is in line with available evidence that the EQ-5D-3L suffers from ceiling effects in milder conditions [37]. Nevertheless, at a WTP of €20.000 for gaining a QALY, the probability of being cost-effective was 71%.

As inpatient costs were reported from only a few participants but were associated with high costs, these costs might have distorted the results. Excluding these costs led to higher ICERs for both outcomes (eg, symptom-free status and QALYs). The probability of being cost-effective rose to 86% and 96% at a

WTP of €0 and €1000 with regard to symptom-free status, and 86% and 90% for gaining a QALY, respectively.

Increasing and subsequently reducing the intervention costs by €100 led to a 66% and 76% probability that the intervention produces a greater health gain at lower costs than WLC with regard to symptom-free status and 1-point improvement.

Discussion

Principal Findings

This study evaluated the cost-effectiveness and cost-utility of a Web-based guided self-help intervention for employees with elevated stress levels aimed at reducing perceived stress compared with WLC from the societal perspective. The intervention had a significant and favorable effect on perceived stress after 6 months and a high probability of being cost-effective compared with the control condition. The overall conclusion of this study does not change when using any of the assumptions, as explored in the sensitivity analyses.

Strengths and Limitations

First, we had missing data, which were handled using imputation techniques to perform an ITT analysis of both effects and costs [60]. As dropout rate was very low (12.8% for the iSMI and 8.33% for the WLC at 6 months), it is unlikely that this has biased the results substantially. Second, the costs and effects were only evaluated over a 6 months period. Hence, we cannot draw any conclusions about long-term effects. Third, self-reported costs and effects might have led to social desirability and/or recall bias. Nonetheless it seems unlikely that this bias differed systematically between groups due to absent baseline differences. Fourth, approaches used for cost estimation of lost productivity are based on the participants' wages which do not reflect the average wages in the general population. Fifth, a waitlist control group design with unrestricted access to treatment as usual was chosen, which causes participants to be less motivated to initiate health-related behavior changes and thus over-accentuates effects [61]. Sixth, the majority of the sample was female, which is a common feature of mental health internet-based interventions [62]. The gender imbalance might limit the generalizability of study findings. Finally, the use of behavioral interventions does not result in improved working conditions that could cause less job strain. However, the potential of workplace-related interventions is often not fully utilized, and hence, such interventions are not systematically implemented. Thus, we recommend a combined implementation to design healthy working conditions.

Comparison With Findings From Other Studies

The results of this study with an effect size of d=0.83 [23] on perceived stress are in line with the meta-analytic evidence (pooled effect size of d=0.43, 95% CI: 0.31-0.54) [16].

In addition, some evidence exists for the economic benefits of stress management and internet-based interventions to reduce depressive symptoms in employees. However, to the best of our knowledge, this study is the first study to evaluate the cost-effectiveness of a Web-based guided self-help intervention for employees with elevated stress levels.

Jacobsen et al evaluated the costs of a self- and professional-administered stress-management intervention not delivered over the internet in patients undergoing chemotherapy compared with usual care [63]. Lower costs and statistically higher quality of life outcomes were found in the intervention group. Hedman et al compared behavioral stress management with iCBT for treatment of severe health anxiety. The iSMI resulted in lower costs but was not considered cost-effective [22].

In a Web-based intervention by Geraedts [64], the probabilities of cost-effectiveness were 0.62 (societal perspective) and 0.55 (employer's perspective) compared with WLC in employees with depressive symptoms. The intervention was not judged cost-effective. Besides that, the reduction of depressive symptoms was rather small (d=0.16) [65] compared with our study (d=0.64) [23] at post measurement. However, Buntrock et al reported an effect size of d=0.69 for a Web-based intervention for the prevention of depression. This intervention has an acceptable likelihood of being more cost-effective than enhanced usual care [21]. Focusing on perceived stress rather than on depressive symptoms in employees seems to be a cost-effective strategy to reduce the mental burden.

Clinical Implications

The results of this study support the idea that iSMIs could be a promising cost-effective strategy in reducing adverse effects of persistent stress in the workplace. Intervention costs were mainly driven by psychologists who acted as e-Coaches. Yet, studies showed that iSMIs are also effective when delivered in a less costly adherence-focused guidance and pure self-help format [33]. However, meta-analytic evidence shows that guidance yields higher effect sizes [66]. Therefore, the cost-effectiveness of guided versus unguided iSMI needs to be evaluated.

Long-term costs caused by persistent stress, such as staff turnover or mental health disorder onsets, were not taken into account. Future studies should investigate the long-term economic effects of iSMIs. The sample consisted predominately of middle-aged women. Future research should focus on the general German working population regarding recruitment, implementation, and dissemination.

Conclusions

This study demonstrated that this iSMI has a high probability of being cost-effective in reducing stress levels when compared with WLC. Given the increasing stress in the workplace and the small number of people who are reached via available health care services [67], it would be worthwhile to integrate such iSMIs into routine occupational health care, which conventionally only consists of face-to-face therapy by occupational health physicians.

Acknowledgments

The authors gratefully acknowledge the contribution of all participants, research assistants, therapists, and all others who contributed to this study. Funding was received from the European Union (project number: EFRE: CCI 2007DE161PR001) and the BARMER (German statutory health insurance company). The funders did not have a role in study design, data collection, analyses or interpretation of the results, or the decision to publicize the study results.

Authors' Contributions

MB obtained the funding for this trial and DDE obtained the funding for the analysis. EH was responsible for the study administration. FK analyzed the data and drafted the manuscript on the health-economic evaluation, and DDE supervised this process. All authors contributed to the further writing of the manuscript and approved the final version of the manuscript.

Conflicts of Interest

DDE, DL, EH, and MB are stakeholders of the "Institute for Online Health Trainings," which aims to transfer scientific knowledge related to this research into routine health care.

Multimedia Appendix 1

Unit costs for the type of health service utilized by the participants.

[PDF File (Adobe PDF File), 14KB-Multimedia Appendix 1]

Multimedia Appendix 2

Demographic characteristics: means/counts, standard deviations/percentages at baseline.

[PDF File (Adobe PDF File), 14KB-Multimedia Appendix 2]

References

1. Eurofound. Developments in Working Life in EuropeurWORK Annual Review. Luxembourg: Publications Office of the European Union; 2016.
2. Siegrist J. Adverse health effects of high-effort/low-reward conditions. J Occup Health Psychol 1996 Jan;1(1):27-41. [doi: 10.1038/372669a0] [Medline: 9547031]
3. Karasek Jr RA. Job demands, job decision latitude, and mental strain: implications for job redesign. Adm Sci Q 1979 Jun;24(2):285-308. [doi: 10.2307/2392498]
4. Åkerstedt T, Orsini N, Petersen H, Axelsson J, Lekander M, Kecklund G. Predicting sleep quality from stress and prior sleep--a study of day-to-day covariation across six weeks. Sleep Med 2012 Jun;13(6):674-679. [doi: 10.1016/j.sleep.2011.12.013] [Medline: 22621983]
5. Theorell T, Hammarström A, Aronsson G, Träskman BL, Grape T, Hogstedt C, et al. A systematic review including meta-analysis of work environment and depressive symptoms. BMC Public Health 2015 Aug 1;15:738 [FREE Full text] [doi: 10.1186/s12889-015-1954-4] [Medline: 26232123]
6. Dragano N, Siegrist J, Nyberg ST, Lunau T, Fransson EI, Alfredsson L, IPD-Work Consortium. Effort–reward imbalance at work and incident coronary heart disease: a multicohort study of 90,164 individuals. Epidemiology 2017 Dec;28(4):619-626 [FREE Full text] [doi: 10.1097/EDE.0000000000000666] [Medline: 28570388]
7. Sihawong R, Sitthipornvorakul E, Paksaichol A, Janwantanakul P. Predictors for chronic neck and low back pain in office workers: a 1-year prospective cohort study. J Occup Health 2016;58(1):16-24 [FREE Full text] [doi: 10.1539/joh.15-0168-OA] [Medline: 26498979]
8. Niedhammer I, Chastang J, Sultan-Taïeb H, Vermeylen G, Parent-Thirion A. Psychosocial work factors and sickness absence in 31 countries in Europe. Eur J Public Health 2013 Aug;23(4):622-629. [doi: 10.1093/eurpub/cks124] [Medline: 23002241]
9. Uegaki K, Bakker I, de Bruijne M, van der Beek A, Terluin B, van Marwijk H, et al. Cost-effectiveness of a minimal intervention for stress-related sick leave in general practice: results of an economic evaluation alongside a pragmatic randomised control trial. J Affect Disord 2010 Jan;120(1-3):177-187. [doi: 10.1016/j.jad.2009.04.012] [Medline: 19439362]
10. Rebergen DS, Bruinvels DJ, van Tulder MW, van der Beek AJ, van Mechelen W. Cost-effectiveness of guideline-based care for workers with mental health problems. J Occup Environ Med 2009 Mar;51(3):313-322. [doi: 10.1097/JOM.0b013e3181990d8e] [Medline: 19225416]
11. Kalia M. Assessing the economic impact of stress--the modern day hidden epidemic. Metabolism 2002 Jun;51(6 Suppl 1):49-53. [doi: 10.1053/meta.2002.33193] [Medline: 12040542]
12. Hassard J, Teoh KR, Visockaite G, Dewe P, Cox T. The cost of work-related stress to society: a systematic review. J Occup Health Psychol 2018 Jan;23(1):1-17. [doi: 10.1037/ocp0000069] [Medline: 28358567]

13. Richardson KM, Rothstein HR. Effects of occupational stress management intervention programs: a meta-analysis. J Occup Health Psychol 2008 Jan;13(1):69-93. [doi: 10.1037/1076-8998.13.1.69] [Medline: 18211170]
14. Hilton MF, Whiteford HA, Sheridan JS, Cleary CM, Chant DC, Wang PS, et al. The prevalence of psychological distress in employees and associated occupational risk factors. J Occup Environ Med 2008 Jul;50(7):746-757. [doi: 10.1097/JOM.0b013e31817e9171] [Medline: 18617830]
15. Griffiths F, Lindenmeyer A, Powell J, Lowe P, Thorogood M. Why are health care interventions delivered over the internet? A systematic review of the published literature. J Med Internet Res 2006;8(2):e10 [FREE Full text] [doi: 10.2196/jmir.8.2.e10] [Medline: 16867965]
16. Heber E, Ebert DD, Lehr D, Cuijpers P, Berking M, Nobis S, et al. The benefit of web-and computer-based interventions for stress: a systematic review and meta-analysis. J Med Internet Res 2017 Feb 17;19(2):e32 [FREE Full text] [doi: 10.2196/jmir.5774] [Medline: 28213341]
17. Donker T, Blankers M, Hedman E, Ljótsson B, Petrie K, Christensen H. Economic evaluations of internet interventions for mental health: a systematic review. Psychol Med 2015 Dec;45(16):3357-3376. [doi: 10.1017/S0033291715001427] [Medline: 26235445]
18. Blankers M, Nabitz U, Smit F, Koeter MW, Schippers GM. Economic evaluation of internet-based interventions for harmful alcohol use alongside a pragmatic randomized controlled trial. J Med Internet Res 2012;14(5):e134 [FREE Full text] [doi: 10.2196/jmir.2052] [Medline: 23103771]
19. Graham AL, Chang Y, Fang Y, Cobb NK, Tinkelman DS, Niaura RS, et al. Cost-effectiveness of internet and telephone treatment for smoking cessation: an economic evaluation of The iQUITT Study. Tob Control 2013 Nov;22(6):e11 [FREE Full text] [doi: 10.1136/tobaccocontrol-2012-050465] [Medline: 23010696]
20. Nordgren LB, Hedman E, Etienne J, Bodin J, Kadowaki A, Eriksson S, et al. Effectiveness and cost-effectiveness of individually tailored internet-delivered cognitive behavior therapy for anxiety disorders in a primary care population: a randomized controlled trial. Behav Res Ther 2014 Aug;59:1-11 [FREE Full text] [doi: 10.1016/j.brat.2014.05.007] [Medline: 24933451]
21. Buntrock C, Berking M, Smit F, Lehr D, Nobis S, Riper H, et al. Preventing depression in adults with subthreshold depression: health-economic evaluation alongside a pragmatic randomized controlled trial of a web-based intervention. J Med Internet Res 2017 Jan 4;19(1):e5 [FREE Full text] [doi: 10.2196/jmir.6587] [Medline: 28052841]
22. Hedman E, Andersson E, Ljótsson B, Axelsson E, Lekander M. Cost effectiveness of internet-based cognitive behaviour therapy and behavioural stress management for severe health anxiety. BMJ Open 2016;6(4):e009327 [FREE Full text] [doi: 10.1136/bmjopen-2015-009327] [Medline: 27113231]
23. Heber E, Lehr D, Ebert DD, Berking M, Riper H. Web-based and mobile stress management intervention for employees: a randomized controlled trial. J Med Internet Res 2016;18(1):e21 [FREE Full text] [doi: 10.2196/jmir.5112] [Medline: 26818683]
24. Husereau D, Drummond M, Petrou S, Carswell C, Moher D, Greenberg D, CHEERS Task Force. Consolidated Health Economic Evaluation Reporting Standards (CHEERS) statement. Br Med J 2013 Mar 25;346:f1049 [FREE Full text] [doi: 10.1136/bmj.f1049] [Medline: 23529982]
25. Ramsey S, Willke R, Briggs A, Brown R, Buxton M, Chawla A, et al. Good research practices for cost-effectiveness analysis alongside clinical trials: the ISPOR RCT-CEA Task Force report. Value Health 2005;8(5):521-533 [FREE Full text] [doi: 10.1111/j.1524-4733.2005.00045.x] [Medline: 16176491]
26. Datinf Randlist - Software to create Randomisation Lists. URL: http://randomisation.eu/ [accessed 2019-04-12] [WebCite Cache ID 77ZhbpKfa]
27. Lesage F, Berjot S, Deschamps F. Psychometric properties of the French versions of the perceived stress scale. Int J Occup Med Environ Health 2012 Jun;25(2):178-184 [FREE Full text] [doi: 10.2478/S13382-012-0024-8] [Medline: 22528542]
28. Malouff JM, Thorsteinsson EB, Schutte NS. The efficacy of problem solving therapy in reducing mental and physical health problems: a meta-analysis. Clin Psychol Rev 2007 Jan;27(1):46-57. [doi: 10.1016/j.cpr.2005.12.005] [Medline: 16480801]
29. Berking M, Ebert D, Cuijpers P, Hofmann SG. Emotion regulation skills training enhances the efficacy of inpatient cognitive behavioral therapy for major depressive disorder: a randomized controlled trial. Psychother Psychosom 2013;82(4):234-245. [doi: 10.1159/000348448] [Medline: 23712210]
30. Ebert D, Lehr D, Heber E, Riper H, Cuijpers P, Berking M. Internet- and mobile-based stress management for employees with adherence-focused guidance: efficacy and mechanism of change. Scand J Work Environ Health 2016 Dec 1;42(5):382-394 [FREE Full text] [doi: 10.5271/sjweh.3573] [Medline: 27249161]
31. Ebert DD, Lehr D, Smit F, Zarski A, Riper H, Heber E, et al. Efficacy and cost-effectiveness of minimal guided and unguided internet-based mobile supported stress-management in employees with occupational stress: a three-armed randomised controlled trial. BMC Public Health 2014;14:807 [FREE Full text] [doi: 10.1186/1471-2458-14-807] [Medline: 25099533]
32. Heber E, Ebert DD, Lehr D, Nobis S, Berking M, Riper H. Efficacy and cost-effectiveness of a web-based and mobile stress-management intervention for employees: design of a randomized controlled trial. BMC Public Health 2013;13:655 [FREE Full text] [doi: 10.1186/1471-2458-13-655] [Medline: 23855376]

33. Ebert DD, Heber E, Berking M, Riper H, Cuijpers P, Funk B, et al. Self-guided internet-based and mobile-based stress management for employees: results of a randomised controlled trial. Occup Environ Med 2016 May;73(5):315-323. [doi: 10.1136/oemed-2015-103269] [Medline: 26884049]
34. Zarski A, Lehr D, Berking M, Riper H, Cuijpers P, Ebert DD. Adherence to internet-based mobile-supported stress management: a pooled analysis of individual participant data from three randomized controlled trials. J Med Internet Res 2016;18(6):e146 [FREE Full text] [doi: 10.2196/jmir.4493] [Medline: 27357528]
35. Jacobson NS, Truax P. Clinical significance: a statistical approach to defining meaningful change in psychotherapy research. J Consult Clin Psychol 1991 Feb;59(1):12-19. [doi: 10.1016/S0005-7894(86)80060-0] [Medline: 2002127]
36. Ware J, Kosinski M, Keller SD. A 12-Item Short-Form Health Survey: construction of scales and preliminary tests of reliability and validity. Med Care 1996 Mar;34(3):220-233. [doi: 10.1097/00005650-199603000-00003] [Medline: 8628042]
37. Brazier J, Roberts J, Tsuchiya A, Busschbach J. A comparison of the EQ-5D and SF-6D across seven patient groups. Health Econ 2004 Sep;13(9):873-884. [doi: 10.1002/hec.866] [Medline: 15362179]
38. Federal Statistical Office of Germany. 2015. Consumer Price Indices URL: https://www.destatis.de/EN/FactsFigures/NationalEconomyEnvironment/Prices/ConsumerPriceIndices/ConsumerPriceIndices.html, [accessed 2016-08-30] [WebCite Cache ID 6k9PhqEof]
39. Van Hakkaart RL, Van Straten A, Donker M, Tiemens B. Manual Trimbos/iMTA Questionnaire for Costs Associated with Psychiatric Illness (TIC-P). Rotterdam: Institute for Medical Technology Assessment; Jan 2002.
40. Bouwmans C, de Jong K, Timman R, Zijlstra-Vlasveld M, van der Feltz-Cornelis C, Tan SS, et al. Feasibility, reliability and validity of a questionnaire on healthcare consumption and productivity loss in patients with a psychiatric disorder (TiC-P). BMC Health Serv Res 2013;13:217 [FREE Full text] [doi: 10.1186/1472-6963-13-217] [Medline: 23768141]
41. Nobis S, Lehr D, Ebert DD, Berking M, Heber E, Baumeister H, et al. Efficacy and cost-effectiveness of a web-based intervention with mobile phone support to treat depressive symptoms in adults with diabetes mellitus type 1 and type 2: design of a randomised controlled trial. BMC Psychiatry 2013;13:306 [FREE Full text] [doi: 10.1186/1471-244X-13-306] [Medline: 24238346]
42. Lin J, Lüking M, Ebert D, Buhrman M, Andersson G, Baumeister H. Effectiveness and cost-effectiveness of a guided and unguided internet-based Acceptance and Commitment Therapy for chronic pain: study protocol for a three-armed randomised controlled trial. Internet Interv 2015 Mar;2(1):7-16 [FREE Full text] [doi: 10.1016/j.invent.2014.11.005]
43. Buntrock C, Ebert DD, Lehr D, Cuijpers P, Riper H, Smit F, et al. Evaluating the efficacy and cost-effectiveness of web-based indicated prevention of major depression: design of a randomised controlled trial. BMC Psychiatry 2014;14:25 [FREE Full text] [doi: 10.1186/1471-244X-14-25] [Medline: 24485283]
44. Thiart H, Ebert DD, Lehr D, Nobis S, Buntrock C, Berking M, et al. Internet-based cognitive behavioral therapy for insomnia: a health economic evaluation. Sleep 2016 Oct 01;39(10):1769-1778 [FREE Full text] [doi: 10.5665/sleep.6152] [Medline: 27450686]
45. Boß L, Lehr D, Berking M, Riper H, Schaub MP, Ebert DD. Evaluating the (cost-)effectiveness of guided and unguided Internet-based self-help for problematic alcohol use in employees--a three arm randomized controlled trial. BMC Public Health 2015 Oct 12;15:1043 [FREE Full text] [doi: 10.1186/s12889-015-2375-0] [Medline: 26458872]
46. Sander L, Paganini S, Lin J, Schlicker S, Ebert DD, Buntrock C, et al. Effectiveness and cost-effectiveness of a guided internet- and mobile-based intervention for the indicated prevention of major depression in patients with chronic back pain-study protocol of the PROD-BP multicenter pragmatic RCT. BMC Psychiatry 2017 Jan 21;17(1):36 [FREE Full text] [doi: 10.1186/s12888-017-1193-6] [Medline: 28109247]
47. Matthews JN, Altman DG, Campbell MJ, Royston P. Analysis of serial measurements in medical research. Br Med J 1990 Jan 27;300(6719):230-235 [FREE Full text] [doi: 10.1136/bmj.300.6719.230] [Medline: 2106931]
48. Bock J, Brettschneider C, Seidl H, Bowles D, Holle R, Greiner W, et al. [Calculation of standardised unit costs from a societal perspective for health economic evaluation]. Gesundheitswesen 2015 Jan;77(1):53-61. [doi: 10.1055/s-0034-1374621] [Medline: 25025287]
49. Krauth C. [Methods of cost determination in the health economic evaluation]. Gesundh ökon Qual manag 2010 Oct 27;15(05):251-259. [doi: 10.1055/s-0029-1245680]
50. Rote Liste. [Red List® 2013 Book Edition - Single Issue: Drug List for Germany (Including EU Approvals and Certain Medical Devices)]. Frankfurt/Main: Rote Liste Service GmbH; 2013.
51. [Income Tax Code]. Berlin: Bundesministerium der Justiz (Federal Office of Justice); 2008.
52. Drummond MF, Sculpher MJ, Claxton K, Stoddart GL, Torrance GW. Methods for the Economic Evaluation of Health Care Programmes, Fourth Edition. Oxford: Oxford University press; 2015.
53. Osterhaus JT, Gutterman DL, Plachetka JR. Healthcare resource and lost labour costs of migraine headache in the US. Pharmacoeconomics 1992 Jul;2(1):67-76. [doi: 10.2165/00019053-199202010-00008] [Medline: 10146980]
54. van Hout BA, Al MJ, Gordon GS, Rutten FF. Costs, effects and C/E-ratios alongside a clinical trial. Health Econ 1994 Oct;3(5):309-319. [doi: 10.1002/hec.4730030505] [Medline: 7827647]
55. Briggs A, Gray A. Handling uncertainty when performing economic evaluation of healthcare interventions. Health Technol Assess 1999;3(2):1-134 [FREE Full text] [Medline: 10448202]

56. Willan AR, Briggs AH, Hoch JS. Regression methods for covariate adjustment and subgroup analysis for non-censored cost-effectiveness data. Health Econ 2004 May;13(5):461-475. [doi: 10.1002/hec.843] [Medline: 15127426]
57. Stata: Release 13. Statistical Software.College Station. TX: StataCorp LP; 2013.
58. EuroQol Group. EuroQol—A new facility for the measurement of health-related quality of life. Health Policy 1990 Dec;16(3):199-208. [doi: 10.1016/0168-8510(90)90421-9] [Medline: 10109801]
59. GesundheitsTraining.Online. URL: http://www.geton-training.de/ [accessed 2019-04-12] [WebCite Cache ID 77Zhlw7La]
60. Buchberger B, Heymann R, Huppertz H, Friepörtner K, Pomorin N, Wasem J. The effectiveness of interventions in workplace health promotion as to maintain the working capacity of health care personal. GMS Health Technol Assess 2011;7:Doc06 [FREE Full text] [doi: 10.3205/hta000097] [Medline: 22031811]
61. Furukawa TA, Noma H, Caldwell DM, Honyashiki M, Shinohara K, Imai H, et al. Waiting list may be a nocebo condition in psychotherapy trials: a contribution from network meta-analysis. Acta Psychiatr Scand 2014 Sep;130(3):181-192. [doi: 10.1111/acps.12275] [Medline: 24697518]
62. Crisp DA, Griffiths KM. Participating in online mental health interventions: who is most likely to sign up and why? Depress Res Treat 2014;2014:790457 [FREE Full text] [doi: 10.1155/2014/790457] [Medline: 24804089]
63. Jacobsen PB, Meade CD, Stein KD, Chirikos TN, Small BJ, Ruckdeschel JC. Efficacy and costs of two forms of stress management training for cancer patients undergoing chemotherapy. J Clin Oncol 2002 Jun 15;20(12):2851-2862. [doi: 10.1200/JCO.2002.08.301] [Medline: 12065562]
64. Geraedts AS, van Dongen JM, Kleiboer AM, Wiezer NM, van Mechelen W, Cuijpers P, et al. Economic evaluation of a web-based guided self-help intervention for employees with depressive symptoms: results of a randomized controlled trial. J Occup Environ Med 2015 Jun;57(6):666-675. [doi: 10.1097/JOM.0000000000000423] [Medline: 25741795]
65. Geraedts AS, Kleiboer AM, Wiezer NM, van Mechelen W, Cuijpers P. Short-term effects of a web-based guided self-help intervention for employees with depressive symptoms: randomized controlled trial. J Med Internet Res 2014 May;16(5):e121 [FREE Full text] [doi: 10.2196/jmir.3185] [Medline: 24800966]
66. Richards D, Richardson T. Computer-based psychological treatments for depression: a systematic review and meta-analysis. Clin Psychol Rev 2012 Jun;32(4):329-342. [doi: 10.1016/j.cpr.2012.02.004] [Medline: 22466510]
67. Levi L. Bridging the science–policy and policy–implementation gaps. In: Cooper CL, Campbell Quick J, editors. The Handbook of Stress and Health: A Guide to Research and Practice. Chichester: John Wiley & Sons; Apr 19, 2017:5-23.

Abbreviations

iCBT: internet-based cognitive behavior therapy
ICER: incremental cost-effectiveness ratio
iSMI: internet-based stress management interventions
ITT: intention-to-treat
PSS-10: Perceived Stress Scale
QALYs: quality-adjusted life years
RCT: randomized controlled trial
WLC: waitlist control condition
WTP: willingness-to-pay

Edited by G Eysenbach; submitted 04.05.18; peer-reviewed by T Donker, Y Lee, P Jimenez; comments to author 30.08.18; revised version received 02.11.18; accepted 30.12.18; published 15.05.19

Please cite as:
Kählke F, Buntrock C, Smit F, Berking M, Lehr D, Heber E, Funk B, Riper H, Ebert DD
Economic Evaluation of an Internet-Based Stress Management Intervention Alongside a Randomized Controlled Trial
JMIR Ment Health 2019;6(5):e10866
URL: https://mental.jmir.org/2019/5/e10866/
doi: 10.2196/10866
PMID: 31094355

Unit costs for the type of health service utilized by the participants.

Health service type	Costs in €[a] per contact
Physician	20.57
Gynecologist	31.27
Orthopedist	25.53
Specialists for internal medicine	63.53
Ophthalmologist	36.55
Dermatologist	19.36
ETN specialist	27.80
Surgeon	44.09
Urologist	25.20
Neurologist	46.49
Psychotherapist	78.53
Dentist	54.62
Logopedics or speech therapy	40.56
Physiotherapy	17.30
Ergotherapy or occupational therapy	39.01
Mean remedies	32.29
	Costs, €[a] per day
General hospital, inpatient	648.11
Mental hospital, inpatient	348.26
General hospital, day patient	421.27
Mental hospital, day patient	226.37
Rehabilitation, outpatient	49.43
Rehabilitation, day patient	93.81
Rehabilitation, inpatient	138.19

[a] Unit costs were calculated for the year 2013 [49] or adjusted by the German consumer price index for 2013

Demographic characteristics: means/counts, standard deviations/percentages at baseline.

	All (N=264),		Internet-based stress management intervention (n=132)		Waitlist control condition (n=132)	
	N (%)	mean (SD)	n (%)	mean (SD)	n (%)	mean (SD)
Sociodemographic Characteristics						
Age	—	43.3 (10.2)	—	42.4 (10.7)	—	44.2 (9.6)
Gender, female, n (%)	193 (73.1)	—	97 (73.5)	—	96 (72.7)	—
Married/Partnership	160 (60.6)	—	80 (60.6)	—	80 (60.6)	—
Experience						
Experience with health trainings	34 (12.9)	—	17 (12.9)	—	17 (12.9)	—
Previous psychotherapy	95 (36.0)	—	52 (39.4)	—	43 (32.6)	—
Current psychotherapy	16 (6.1)	—	5 (3.8)	—	11 (8.3)	—
Work Characteristics						
Years of work experience	—	18.1 (11.1)	—	17.2 (10.8)	—	18.9 (11.2)
Full—time employed	204 (77.3)	—	105 (79.5)	—	99 (75.0)	—
Part—time employed	57 (21.6)	—	25 (18.9)	—	32 (24.2)	—
On sick leave	3 (1.1)	—	2 (1.5)	—	1 (0.8)	—
Work sectors						
Social	97 (36.7)	—	48 (36.4)	—	49 (37.1)	—
Service	43(16.3)	—	21 (15.9)	—	22 (16.7)	—
Health	36 (13.6)	—	22 (16.7)	—	14 (10.6)	—
Economy	31 (11.7)	—	14 (10.6)	—	17 (12.9)	—
IT	15 (5.7)	—	8 (6.1)	—	7 (5.3)	—
Others	42 (16.0)	—	19 (14.3)	—	23 (17.4)	—

3.6 Article 6: Systematic Review of Cost-Effectiveness in IMIs

Authors: Fanny Kählke, Claudia Buntrock, Filip Smit, Daniel D. Ebert
Title: Systematic review of economic evaluations for Internet- and mobile-based interventions for mental health problems
Journal: *NPJ Digital Medicine* (Manuscripts accepted for publication
PROSPERO: CRD42018093808

The high global prevalence of mental disorders poses an enormous economic burden on society. Internet and mobile-based interventions (IMIs) are scalable and of flexible use, yet evidence of their cost-effectiveness for the treatment of mental disorders is inconclusive and outdated and thus unclear. The aim of this review was to 1) systematically review the evidence presented in economic evaluations of psychological IMIs for the treatment or prevention of mental disorders and associated symptoms and to 2) evaluate the methodological study quality. The available literature was systematically screened for economic evaluations alongside randomized controlled trials published prior to May 10th, 2021. Electronic databases (including MEDLINE, PsycINFO, CENTRAL, PSYNDEX and National Health Service Economic Evaluations Database) were searched for psychological IMIs targeting mental disorders and symptoms that employed a full health economic evaluation comparing cost and effects of two of more groups. Methodological quality and risk of bias was assessed via the Consensus on Health Economic Criteria (CHEC) and the Cochrane Collaboration's tool for assessing risk of bias. Cost-effectiveness was assumed at or below £30,000 per quality-adjusted life year gained. In total, 4,042 studies were found and 36 economic evaluations reviewed. The findings showed that guided IMIs accompanied by a therapist or eCoach are likely to be cost-effective in targeting depression and anxiety. The quality of most evaluations was good, albeit with some risk of bias. Heterogeneity across studies was high due to, e.g., different costing methods, design, comparison groups and outcomes, populations, methods, and settings used. In conclusion, IMIs for anxiety and depression have the potential to be cost-effective. Yet, the evidence for unguided self-help interventions in treatment and prevention is scarce. Additionally, more research on IMIs compared to active control conditions, such as face-to-face therapy, treatment as usual, or other interventions over a longer time horizon and across a wider range of disorders, is needed.

The manuscript was submitted in July and accepted in September 2022 in *NPJ Digital Medicine*. It is included as an uncorrected proof. This journal is an online open-access journal dedicated to publishing high quality peer-reviewed research in all aspects of digital medicine.

Contribution: Fanny Kählke was the principal investigator and author of the published article. Fanny Kählke, Claudia Buntrock, and David D. Ebert were involved in the concept and design of the study. Fanny Kählke and Claudia Buntrock were the primary contributors to data extraction and analysis. Fanny Kählke wrote the first draft of the manuscript supervised by Claudia Buntrock and Filip Smit. All co-authors read, critically revised, and finally approved the published article.

npj | digital medicine

www.nature.com/npjdigitalmed

ARTICLE OPEN

Systematic review of economic evaluations for internet- and mobile-based interventions for mental health problems

Fanny Kählke[1]✉, Claudia Buntrock[2], Filip Smit[3,4,5] and David Daniel Ebert[1]

In view of the staggering disease and economic burden of mental disorders, internet and mobile-based interventions (IMIs) targeting mental disorders have often been touted to be cost-effective; however, available evidence is inconclusive and outdated. This review aimed to provide an overview of the cost-effectiveness of IMIs for mental disorders and symptoms. A systematic search was conducted for trial-based economic evaluations published before 10th May 2021. Electronic databases (including MEDLINE, PsycINFO, CENTRAL, PSYNDEX, and NHS Economic Evaluations Database) were searched for randomized controlled trials examining IMIs targeting mental disorders and symptoms and conducting a full health economic evaluation. Methodological quality and risk of bias were assessed. Cost-effectiveness was assumed at or below £30,000 per quality-adjusted life year gained. Of the 4044 studies, 36 economic evaluations were reviewed. Guided IMIs were likely to be cost-effective in depression and anxiety. The quality of most evaluations was good, albeit with some risks of bias. Heterogeneity across studies was high because of factors such as different costing methods, design, comparison groups, and outcomes used. IMIs for anxiety and depression have potential to be cost-effective. However, more research is needed into unguided (preventive) IMIs with active control conditions (e.g., treatment as usual) and longer time horizon across a wider range of disorders.

Trial registration: PROSPERO Registration No. CRD42018093808.

npj Digital Medicine (2022)5:175 ; https://doi.org/10.1038/s41746-022-00702-w

INTRODUCTION

Mental disorders (MDs) are highly prevalent worldwide[1]. Globally, every fifth person is affected, and roughly one-third of adults have experienced mental illness at least once[2]. MDs constitute a substantial burden for individuals and society. Meta-analytic evidence shows an elevated risk of mortality in people with MDs[3,4] and low quality of life[5]. In addition, MDs appear to be correlated with several physical illnesses[6] such as stroke, pain, cancer, diabetes mellitus, asthma, heart disease, hypertension, and insomnia[7]. According to the World Health Organization, disease burden as expressed in disability-adjusted life years (DALYs) associated with MDs is substantial and has remained constant over time and across countries[8]. In 2016, Vigo et al. argued that the "true" estimate of the global burden caused by MDs will double compared with earlier estimates and will account for 13% of total DALYs. Hence, the burden of MDs is comparable with those of cardiovascular and circulatory diseases[9].

MDs are associated with substantial economic costs for society. Associated productivity losses due to absenteeism and presenteeism, earlier retirement, and increased level of healthcare utilization have major influence on society. In 2010, the global costs associated with MDs were estimated at US$2.5 trillion[10]. Indirect costs, such as productivity losses or premature death, were twice as high as direct medical costs related to health service use. In the EU, MD-associated costs are estimated at €798 billion in 2010[11]. However, costs are expected to double by 2030[10] because of increasing demand and rising costs.

Despite the availability of effective psychological interventions[12], the majority of individuals with MDs remain untreated[13] or receive delayed treatment often initiated several years after MD onset[14]. The reasons are multifaceted. Attitudinal barriers, such as low perceived need or a stigma-related desire to handle one's problems seems to be more important than structural barriers, such as availability of treatment and expenses both for initiating and continuing treatment[15]. One promising approach to overcome these barriers of traditional psychological interventions are internet- and mobile-based interventions (IMIs). IMIs can address these barriers, as IMIs are anonymous, effective, and accessible 24/7[16,17]. Additionally, IMIs can be implemented as stand-alone self-help interventions, as blended care (a face-to-face therapy extended with psychoeducation delivered via the internet) or as part of a stepped care approach in which the amount of support is adjusted to the patient's needs. IMIs were shown to be effective for treating common MDs across various settings and age groups[18–20].

Although the initial costs of developing IMIs can be substantial, the low marginal costs of providing IMIs to additional users can result in lower overall expenditure because of an economies of scale effect[16]. However, intervention costs largely vary based on the following four aspects: development phase (new product vs. modified version), scaling-up effects (small vs. large number of users), overestimation of costs (small number of study participants), and efficiency (improving productivity vs. additional costs when newly implemented)[21]. In addition, IMIs are likely to reduce healthcare costs compared

[1]Department of Sport and Health Sciences, Professorship of Psychology and Digital Mental Health Care, Technische Universität München, Munich, Germany. [2]Institute of Social Medicine and Health Systems Research, Medical Faculty, Otto-von-Guericke-University, Magdeburg, Germany. [3]Department of Clinical, Neuro and Developmental Psychology, Amsterdam Public Health Research Institute, Vrije Universiteit, Amsterdam, The Netherlands. [4]Department of Epidemiology and Biostatistics, Amsterdam Public Health Research Institute, Amsterdam University Medical Centers, Location VUmc, Amsterdam, The Netherlands. [5]Centre of Health-Economic Evaluation, Trimbos Institute (Netherlands Institute of Mental Health and Addiction), Utrecht, The Netherlands. ✉email: fanny.kaehlke@tum.de

with traditional face-to-face treatment, as IMIs reduce costs stemming from therapist's time and patient's travel to health services[22]. Hence, IMIs are often touted to be cost-effective despite the weak evidence base for their cost-effectiveness.

Several systematic reviews have attempted to establish the cost-effectiveness of IMIs for MDs in comparison with various control groups. However, the presented evidence on whether IMIs for MDs provide good value for money is inconclusive because some reviews included only few internet-based studies: $n = 3$[23], $n = 4$[24], $N = 12$[25], $n = 1$[26], and $n = 5$[27]. In addition, 6 of 8 reviews can be considered obsolete today with the latest primary study stemming from 2016[22–25,27,28], whereas many more studies have since been published, e.g., 26 identified ongoing cost-effectiveness studies for major depression[25]. Moreover, previous reviews used broad definitions of IMIs, e.g., any internet or web enabled platform for diagnosis, screening, treatment, prevention, training, education, or facilitating self-management of MDs[29]. Finally, previous reviews have not always included full health economic evaluations, but have reported costs and effects without relating them to each other[23,29], and if they did, they only focused on internet-based cognitive behavioral therapy (iCBT)[22]. Likewise, there exist only a few economic evaluations for common treatment options (different types of psychotherapy, pharmacological interventions, such as antidepressants) for depression[30] and anxiety disorders[24]. Some evidence shows that psychotherapy might be cost-effective compared with pharmacological interventions.

Therefore, a comprehensive overview of the state-of-the-art evidence of IMIs across MDs and symptoms including studies with good methodological quality and full economic evaluations are needed to enable better comparisons and obtain reliable conclusions on guidance, cost perspective, and psychological interventions other than iCBT.

In view of the disease and economic burden of MDs, first, we evaluated whether IMIs for the prevention and treatment of common MDs represent good value for money. Second, we assessed whether these interventions have a good methodological quality. In this respect, our review provides additional evidence to decision makers[31] to make informed decisions on the allocation of scarce resources to provide sustainable healthcare.

RESULTS

Study selection

A total of 4044 articles were identified, of which 2951 duplicates and non-relevant studies were removed. Of the 277 full text articles, 36 were eligible for inclusion (Fig. 1), referring to 32 studies. One study was assessed by three articles, and two studies were assessed by two articles. These articles differed by perspectives taken[32–35], time horizons used[36,37], or type of analysis[36,38] used for the evaluation.

Study characteristics

Table 1 lists relevant study characteristics. Of the 32 studies, 5 have 3 and 1 has 4 comparison groups, whereas 27 only compare 2 groups. In three studies, the same IMI was evaluated[39–42]. The included studies encompassed a total of 10,083 participants. The studies were published between 2010 and 2021 and originated from Australia ($n = 2$), Canada ($n = 1$), Germany ($n = 7$), Netherlands ($n = 8$), United Kingdom ($n = 6$), Spain ($n = 1$), and Sweden ($n = 10$). On average, studies were published in 2015, and most studies were published in 2014 ($n = 7$) and 2017 ($n = 6$). All studies targeted an adult population, except for four studies that were either directed at adolescents (aged 12–19 years, $n = 2$) or people aged >65 years ($n = 2$). Participants were recruited from primary care ($n = 3481$), workplace ($n = 1260$), general population ($n = 4581$), or a mixed setting ($n = 1057$, primary/secondary care and general population). Most of the participants were female ($n = 7282$; 72%) and aged 40 years (mean age 42, SD = 13). The majority of the studies targeted major depressive disorder (MDD) or depressive symptoms ($n = 15$), followed by anxiety disorders ($n = 7$), and obsessive-compulsive disorder (OCD, $n = 4$).

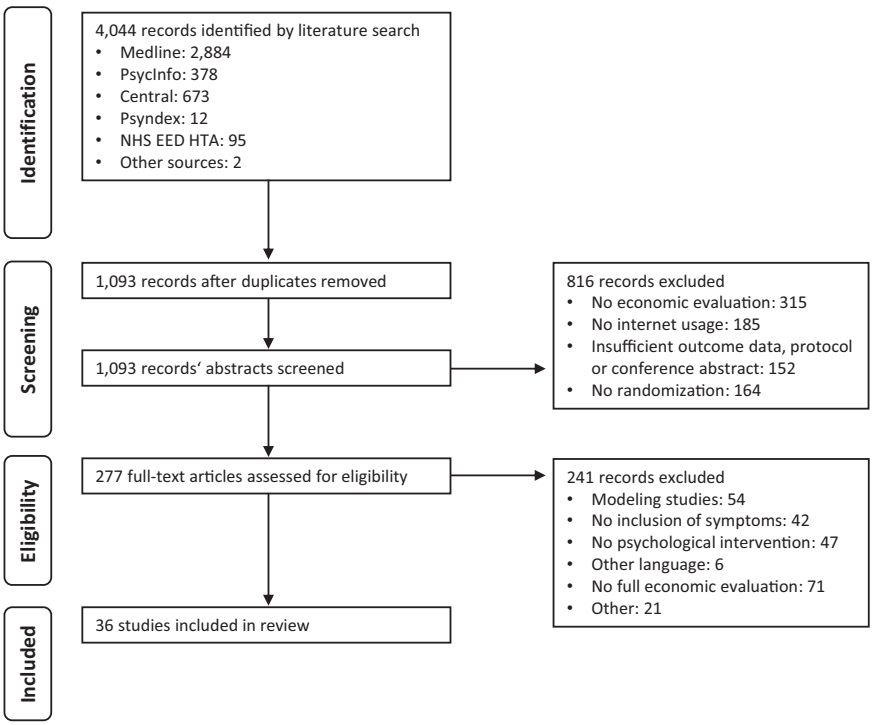


Fig. 1 PRISMA flow diagram. Using the Preferred Reporting Items for Systematic Reviews and Meta-Analyses as a screening process, a total of 36 studies were included in the study.

Table 1. Study characteristics.

Study ID	Author ref., country	Disorder target	Setting/sample	Type of evaluation	Sample size (*N*)	Mean age (SD)	Gender (%, female)	Trial arms (*N*)	Delivery period, weeks (sessions)	Guidance	Time horizon
Treatment of subthreshold depression/minor depression/depressive symptoms											
1	Bolier et al.[48], NL	Depressive symptoms	General population Mild to moderate depressive symptoms (CES-D: 10–24)	CEA	284	43.2 (11.8)	80	iPPI (143) WLC (141)	8 (6)	Unguided	6 months[a]
2	Buntrock et al.[43], GER	Depressive symptoms	General population Some depressive symptoms (CES-D ≥ 16), but no MDE (SCID-I)	CEA, CUA	406	45 (11.9)	74	iCBT (202) TAU^{+} (204)	6 (6)	Guided	12 months
3	Gerhards et al.[50], NL	Depressive symptoms	General population At least mild to moderate depressive symptoms (BDI-II score ≥16)	CEA, CUA	303	44.9 (11.6)	57	iCBT (100) iCBT and TAU (100) TAU (103)	8 (8 + 1)	Unguided	12 months
4	Phillips et al.[41], UK	Depressive symptoms	Workplace, Moderate to severe depressive symptoms, PHQ-9 >scored 2 or more on item 1 and 2 and in total on 5 items	CUA	637	42.5 (9.6)	53	iCBT (318) AC (319)	5 (5)	Unguided	6 weeks
5	Titov et al.[56], AUS	Depressive symptoms	General population Adults >60 years, "report feeling depressed"	CUA	54	65.4 (3.2)	73	iCBT (29) WLC (25)	8 (5)	Guided	8 weeks
6	Van Luenen et al.[55], NL	Depressive symptoms	Primary care People with HIV, PHQ-9 score >4 and <20 (mild to moderate symptoms)	CUA	188	46 (10.63)	88	AC + WLC (91) iCBT (97)	8 (8)	Guided	6 months
Treatment of major depression disorder											
7	Brabyn et al.[39], UK	Depression	Primary care PHQ-9 score ≥10 (cut-off point to detect major depression)	CUA	369	40.6 (13.8)	65	iCBT + uGPC (187) iCBT + uGPC (182)	6 (6)	Guided Unguided	12 months
8	Geraedts et al.[52], NL	Depression	Workplace At least mild depressive Symptoms (CES-D score ≥16)	CBA, CEA, CUA	231	43.4 (9.0)	62	iPST (116) TAU (115)	6–7 (6)	Guided	12 months
9	Hollinghurst et al.[54], UK	Depression	Primary care ICD-10 diagnosis of depression (CIS-R), and a BDI score ≥14	CEA, CUA	297	34.9 (11.6)	68	iCBT (149) WLC (148)	16 (10)	Guided	8 months
10	Klein et al.[44], NL	Recurrent depression	Mixed sample remitted (at least 2 months) individuals with recurrent MDD (last 2 years, SCID-I) and score of ≤10 on HRSD	CEA, CUA	264	46 (10.8)	75	iPCT + TAU (132) TAU (132)	8 (8)	Guided	24 months

Table 1 continued

Study ID	Author ref., country	Disorder target	Setting/sample	Type of evaluation	Sample size (*N*)	Mean age (SD)	Gender (%, female)	Trial arms (*N*)	Delivery period, weeks (sessions)	Guidance	Time horizon
11	Littlewood et al.[40], UK	Depression	Primary care PHQ-9 score ≥10	CUA	691	39.8 (12.6)	67	iCBT 1 + uGPC (210) iCBT 2 + uGPC (242) uGPC (239)	iCBT 1 8 (8) iCBT 2 8 (6)	Unguided Unguided	24 months
12	Nobis et al.[51], GER	Depression	General population Participants with moderate to severe depressive symptoms (CES-D score ≥23, SCID-I) and diabetes mellitus I or II	CEA, CUA	260	51 (12)	63	iCBT (130) TAU^{+} (130)	6–8 (6–8 + 1)	Guided	6 months
13	Romero-Sanchiz et al.[57], SP	Depression	Primary care Mild or moderate depressive symptoms (BDI-II score 14–28)	CEA, CUA	296	42.9 (10.3)	76	iCBT (98) iCBT (96) TAU^{+} (102)	10 (10)	Guided Unguided	12 months
14	Warmerdam et al.[53], NL	Depression	General population Presence of depressive symptoms (CES-D score ≥16)	CEA, CUA	263	45 (12.1)	71	iCBT (88) iPST (88) WLC (87)	8 (8 + 1) 5 (5)	Guided Guided	3 months
15	Yan et al.[49], CAN	Depression	Primary care PHQ-9 score ≥10	CUA	1407	47 (17.0)	73	iCBT (415) SC (412) TAU (397) SCP (183)	5(5)	Unguided	12 months[b]
Treatment of anxiety disorders											
16	Bergström et al.[45], SW	Panic disorder	Mixed sample DSM-IV criteria for panic disorder with or without agoraphobia as primary diagnosis	CEA	113	34.2 (9.5)	62	iCBT ($n = 53$) gCBT ($n = 60$)	10 (10)	Guided	6 months
17	Dear et al.[59], AUS	Anxiety (GAD)	General population Adults >60 years and difficulties with anxiety (self-report)	CUA	72	65.5 (5.3)	60	iCBT (35) WLC (37)	8 (8)	Guided	8 weeks
18	Nordgren et al.[46], SW	Anxiety	Primary care DSM-IV, criteria for any anxiety disorder as a primary diagnosis	CEA, CUA	100	35 (13)	63	iCBT (50) AC	10 (7–10)	Guided	10 weeks
19	Hedman et al.[58], SW	Health anxiety	Mixed sample Primary diagnosis of health anxiety based on diagnostic interview according to DSM-IV	CEA, CUA	81	39.1 (9.7)	74	iCBT (40) AC (41)	12 (12)	Guided	3 months
20	Hedman et al.[60], SW	Health anxiety	General population Severe health anxiety, diagnostic assessment using MINI	CEA, CUA	158	41.6 (13.4)	79	iCBT (79) iMA (79)	12 (12)	Unguided Unguided	3 months

Table 1 continued

Study ID	Author ref., country	Disorder target	Setting/sample	Type of evaluation	Sample size (*N*)	Mean age (SD)	Gender (%, female)	Trial arms (*N*)	Delivery period, weeks (sessions)	Guidance	Time horizon
21, 22 and 23	Hedman et al.[36,37], Alaoui et al.[38], SW	Social anxiety	Mixed sample Diagnostic interview (SCID-I), DSM-IV assessed social anxiety	CEA, CUA, CMA	126	35.4 (11.4)	36	iCBT (64) gCBT (62)	15 (15)	Guided	6 months, 4-year FU
24	Powell et al.[61], UK	Social anxiety	General Population SPIN-17 score ≥13	CUA	2122	37(13.8)	80	iCBT (1061) WLC (1061), both with access to usual care	6(6)	Unguided	12 months
25	Andersson et al.[63], SW	OCD	General population Patients after 10 weeks iCBT, meeting the criteria for OCD DSM-IV-TR and Y-BOCS: 12–31	CEA, CUA	101	34 (13.04)	66	iCBT (50) AC (51)	10 (10)	Guided	10 weeks
26	Andersson et al.[64], SW	OCD	General population Patients after 10 weeks iCBT, meeting the criteria for OCD (DSM-IV-TR) and Y-BOCS: 12–31	CEA	93	36.9 (12.8)	63	iCBT booster session (47) TAU (46)	10 (10)	Guided	2 years[c]
27	Lenhard et al.[65], SW	OCD	General population Adolescents aged 12–17, moderate to severe symptoms of OCD, CY-BOCS score ≥16)	CEA, CUA	67	14.6 (1.71)	46	iCBT (33) WLC (34)	12 (12)	Guided	3 months
28	Lovell et al.[66], UK	OCD	Mixed sample Meeting the criteria for OCD (DSM-IV) and moderate to severe symptoms (Y-BOCS score ≥16)	CUA	473	35.86 (12.4)	60	iCBT (157) Self-help workbook[d] (158) WLC (158)	12 (9)	Guided Guided	3 months[e]
29	Röhr et al.[62], GER	Posttraumatic Stress	Primary Care Syrian refugees with mild to moderate post-traumatic stress symptoms (PDS-5 score, range 11–59)	CUA	133	33.0 (11.0)	53	iCBT (65) TAU^{+}(68)	4 (2)	Unguided	4 months
Treatment of other disorders											
30	De Bruin et al.[67], NL	Insomnia	General population Adolescents aged 12–19 years), DSM-IV criteria for insomnia	CEA, CUA	62	15.5 (1.7)	77	iCBT (31) gCBT (31)	6 (6 + 1)	Guided	12 months
31 and 32	Thiart et al.[35], GER Buntrock et al.[34], GER	Insomnia	Workplace School teacher with clinically significant insomnia (ISI > 14 and work-related rumination (CI > 14)	CBA, CEA, CUA	128	48.0 (9.9)	74	iCBT (64) + TAU WLC (64) + TAU	6 (6)	Guided	6 months

Table 1 continued

Study ID	Author ref., country	Disorder target	Setting/sample	Type of evaluation	Sample size (*N*)	Mean age (SD)	Gender (%, female)	Trial arms (*N*)	Delivery period, weeks (sessions)	Guidance	Time horizon
33 and 34	Ebert et al.[32], Kählke et al.[33], GER	Perceived stress	Workplace Employees with elevated symptoms of perceived stress (PSS-10 ≥ 22)	CBA, CEA, CUA	264	43.4 (10.2)	73	iMA (132) WLC (132)	7 (7)	Guided	6 months
35	Lindsäter et al.[68], SW	Stress-related disorders	General population Adjustment or exhaustion disorder (MINI)	CEA, CUA	100	47 (8.8)	85	iCBT (50) WLC (50)	12 (12)	Guided	3 months
36	Van Spijker et al.[70], NL	Suicidal ideation	General population Mild to moderate suicidal thoughts (1–26 on BSS)	CEA	236	40.93 (13.7)	66	iCBT (116) WLC^{+} (120)	6 (6)	Unguided	6 weeks[a]

AC attention control group, *AUS* Australia, *BA* behavioral activation, *BDI* Beck's Depression Inventory, *BSS* Beck Scale for Suicide Ideation, *CAN* Canada, *CBA* cost-benefit analysis, *CEA* cost-effectiveness analyses, *CES-D* Center of Epidemiologic Studies Depression Scale, *CIS-R* Clinical Interview Schedule-Revised, *CMA* cost-minimization analysis, *CORE-OM* Clinical Outcomes in Routine Evaluation—Outcome Measure—Generic psychological well-being, *CUA* cost-utility analyses, *CR* cognitive Irritation, *CY-BOCS* Children's Yale-brown obsessive-compulsive scale, *DSM-IV* Diagnostic and Statistical Manual of Mental Disorders Fourth Edition, *DSM-V* Diagnostic and Statistical Manual of Mental Disorders Fifth Edition, *F2F* face-to-face, *FU* follow-up, *GAD* generalized anxiety disorder, *gCBT* group-administered cognitive-behavioral therapy, *GER* Germany, *HAI* Health Anxiety Inventory, *HRSD* Hamilton Rating Scale for Depression, *iCBT* internet-based cognitive behavioral therapy, *ICD* International Classification of Diseases, *iMA* internet-based interventions applying mixed approaches, *iPPI* internet-based Positive Psychology Intervention, *iPST* internet-based problem-solving therapy, *iPCT* internet-based preventive cognitive therapy, *ISI* Insomnia Severity Index, *LSAS* Liebowitz Social Anxiety Scale, *MDD* major depressive disorder, *MINI* Mini International Neuropsychiatric Interview, *NL* Netherlands, *NR* not reported, *OCD* obsessive-compulsive disorder, *PDS-5* Posttraumatic Diagnostic Scale for DSM-5, *PDSS* Panic Disorder Severity Scale, *PHQ-9* Patient Health Questionnaire-9, *PSS-10* Perceived Stress Scale, *SCID* Structural Clinical Interview for DSM, *SC* Standard Care, *SCP* stepped care pathway, *SCID* Structural Clinical Interview for DSM, *SE* subjective sleep efficiency, *SP* Spain, *SPIN-17* Social Phobia Inventory, *SW* Sweden, *TAU* treatment as usual, *TAU*$^{+}$ treatment as usual with access to treatment as usual in a more structured obligatory way (e.g., online website following treatment guidelines, offer the general practitioner (GP) training session following guidelines or informing GP about study and control condition in order to increase usual care), *uGPC* Usual General Practitioner Care, *UK* United Kingdom, *WLC* wait list control condition, *WLC+* WLC with additional information during the waiting period, *Y-BOCS* Yale-Brown Obsessive-Compulsive Scale.

[a]Costs collected over short period of time and then annualized.

[b]Utility score assessed over 12 weeks were assumed to be consistent at 12 months.

[c]Participants in the IG (Andersson et al.,[63]) received an iCBT treatment over 10 weeks, the CG received the iCBT after the 10 weeks (crossover). After a 4-month follow-up half of the participants were randomized to receive an additional booster session, 8 and 20 months after randomization to booster session.

[d]Guided self-help consisted of a self-help book: Overcoming OCD: A Workbook, written by the trial team. Participants received weekly guidance from a PWP for one initial session of 60 min (either face to face or by telephone, depending on patient preference) followed by up to ten 30-min sessions over a 12-week period.

[e]After 3 months all three groups had access to high intensity CBT (f2f), therefore only the 3 months' time point was reported.

Table 2. CHEC quality assessment.

Item		Study ID																		
		1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18
(a) (articles 1–18)																				
1	Is the study population clearly described?	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
2	Are competing alternatives clearly described	1	1	1	0	1	1	1	1	1	1	1	1	1	1	1	1	1	1
3	Is a well-defined research question posed in answerable form?	1	1	1	0	1	1	1	1	1	1	1	1	1	1	1	1	1	0.5
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	1
6	Is the chosen time horizon appropriate include relevant costs and consequences?	0.5	1	1	0	0	1	1	1	1	1	1	0.5	1	0	1	1	0	0
7	Is the actual perspective chosen appropriate?	1	1	1	0	1	1	1	1	1	1	1	1	1	1	0.5	0	0	0
8	Are all important and relevant costs for each alternative identified?	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	0	1	1
9	Are all costs measured appropriately in physical units?	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
10	Are costs valued appropriately?	1	1	1	0	0.5	1	1	1	1	1	1	1	1	1	1	0	1	0
11	Are all important and relevant outcomes for each alternative identified?	1	1	1	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	1
13	Are outcomes valued appropriately?	-	1	1	1	1	1	1	1	1	1	1	1	1	1	0	-	1	1
14	Is an incremental analysis of costs and outcomes of alternatives performed?	1	1	0	0	1	1	1	1	1	1	1	1	1	1	1	1	1	1
15	Are all future costs and outcomes discounted appropriately?	-	-	-	-	-	-	-	-	-	1	1	-	-	-	-	-	-	-
16	Are all important variables, whose values are uncertain, appropriately subjected to sensitivity analysis?	1	1	1	0	0.5	1	1	1	0.5	1	1	1	0	1	1	0.5	0.5	1
17	Do the conclusions follow from the reported data?	1	1	1	1	1	1	0.5	1	1	1	1	0.5	0	1	1	1	1	1
18	Does the study discuss the generalizability of the results to other settings and patient/client groups?	0.5	1	0.5	0	0	0	0	0	0.5	1	0.5	0	0.5	0	0	0	0.5	0
19	Does the article indicate that there is no potential conflict of interest of study researcher(s) and funder(s)?	1	1	1	1	1	1	1	1	0.5	1	1	1	1	1	1	1	1	0.5
20	Are ethical and distributional issues discussed appropriately?	1	1	0	0	0	1	0	0	0.5	1	0	0	0	0	1	0	0	0
Score %[a]		94	100	86	56	78	94	86	89	89	100	92	83	81	83	86	68	78	67
(b) (articles 19–36)																				
		19	20	21	22	23	24	25	26	27	28	29	30	31	32	33	34	35	36
1	Is the study population clearly described?	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
2	Are competing alternatives clearly described	1	1	1	1	1	1	0,5	1	1	1	1	1	1	1	1	1	1	1
3	Is a well-defined research question posed in answerable form?	0.5	1	1	1	1	0.5	0.5	0.5	1	1	1	1	1	1	1	1	1	1
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	1
6	Is the chosen time horizon appropriate include relevant costs and consequences?	0	0	0.5	1	1	1	0	1	0	0.5	1	1	1	1	0.5	0.5	0.5	0
7	Is the actual perspective chosen appropriate?	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
8	Are all important and relevant costs for each alternative identified?	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
9	Are all costs measured appropriately in physical units?	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
10	Are costs valued appropriately?	1	1	1	0	1	1	1	0.5	1	1	0.5	1	1	1	1	1	1	1
11	Are all important and relevant outcomes for each alternative identified?	1	1	1	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	1
13	Are outcomes valued appropriately?	1	1	1	1	1	1	1	-	1	1	1	1	-	1	-	1	1	-
14	Is an 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	1	1
15	Are all future costs and outcomes discounted appropriately?	-	-	-	0	1	-	-	0	-	-	-	-	-	-	-	-	-	-
16	Are all important variables, whose values are uncertain, appropriately subjected to sensitivity analysis?	1	0.5	1	1	1	0	0.5	0.5	1	1	0	1	1	1	1	1	1	1

Table 2 continued

Item		Study ID																	
		1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18
17	Do the conclusions follow from the reported data?	1	0	1	1	1	1	0.5	1	1	1	1	1	1	1	1	1	1	1
18	Does the study discuss the generalizability of the results to other settings and patient/client groups?	1	0.5	0.5	0	0.5	0	1	0.5	0.5	0.5	0.5	0	0.5	1	0	0	1	0.5
19	Does the article indicate that there is no potential conflict of interest of study researcher(s) and funder(s)?	1	1	1	1	1	1	0	1	1	1	1	1	1	1	1	1	1	1
20	Are ethical and distributional issues discussed appropriately?	0	0	0.5	0	0	1	0	0	0.5	0.5	1	0	0	1	0	0	1	0.5
Score %[a]		86	78	92	79	92	86	72	78	89	92	89	89	91	100	85	86	97	88

The item number 5 of the CHEClist is excluded because it only applies to modeling studies. 0 no, 0.5 suboptimal, 1 yes.
[a]Score expressed as percentage of the maximum score.

Other studies have evaluated sleep disorders ($n = 2$), elevated stress levels ($n = 2$), posttraumatic stress disorder (PTSD, $n = 1$), and suicidal ideation ($n = 1$). Most studies evaluated guided ($n = 21$) or unguided ($n = 9$) interventions, and only two evaluated both guided and unguided IMIs. Most IMIs were based on iCBT ($n = 35$), problem-solving therapy (iPST; $n = 3$), mixed approaches combining different aspects such as problem-solving and emotion regulation (iMA; $n = 2$), positive psychology (iPPI; $n = 1$), and preventive cognitive therapy (iPCT, $n = 1$). On average, an intervention consisted of 7.9 (2–15) sessions and was most often compared with a wait-listed control group (WLC; $n = 12$). Further details of the studies are presented in Table 1.

Most studies ($n = 16$) conducted both a cost-effectiveness analysis (CEA) and a cost-utility analysis (CUA). Other studies focused solely on either CUAs ($n = 10$) or CEAs ($n = 4$). Three studies conducted a cost-benefit analysis (CBA) in addition to CEA and CUA. The included studies differed in perspectives taken: societal ($n = 15$), healthcare ($n = 6$), and both perspectives ($n = 9$). In the remaining studies, the employer's perspective ($n = 3$) alone or in combination with other perspectives were applied. One study conducted a cost-minimization analysis (CMA). Three studies did not report the study perspective. The time horizon of the follow-ups varied across studies ranging from ≤3 months ($n = 12$), >3 to ≤6 months ($n = 8$), >6 to ≤12 months ($n = 9$) to 2 years ($n = 4$).

Quality assessment

Table 2 contains the Consensus on Health Economic Criteria (CHEC) quality scores. The quality of studies was mainly good (average total score = 85%, range 56–100%). Three studies met all CHEC criteria[34,43,44], whereas three studies showed average quality[41,45,46]. Common reasons for the lower quality were the lack of reporting on the generalizability of the results ($n = 29$), an insufficient time horizon ($n = 16$), or lack of sensitivity analyses ($n = 8$). All studies met the items on appropriateness of the economic study designs and outcome measurement.

Regarding risk of bias (RoB), most studies showed good ($n = 22$), and only a few studies showed fair ($n = 10$) or poor ($n = 4$) quality (Fig. 2 and Table 3). Detection, attrition, and selection bias were low. By contrast, reporting bias ($n = 9$) and other biases were high ($n = 14$). Selective reporting may arise when outcomes for a CEA are not sufficiently described in study protocols and outcome paper. Other biases may arise when there are insufficient information or limitations because of the high complexity of assessing outcomes, e.g., the annualization of short term costs. The agreement for CHEC and RoB between the two raters with Cohen's kappa (κ) = 0.90–0.91 can be considered almost perfect[47].

Findings of included studies

Supplementary Table 1 displays the following characteristics and outcomes for each of the included health economic evaluations: perspective taken, cost categories used, type of health outcome and measurements, mean incremental cost-effectiveness ratio (ICER) or cost-utility ratio (ICUR) and its position in the quadrant of the cost-effectiveness plane, and probabilities of the intervention being cost-effective given various willingness to pay (WTP) thresholds. This table lists all costs in national currency units and for the index year as published by the primary studies. In the next section, probabilities are only listed if reported in the studies: CUA, WTP threshold of £30.000 per QALY gained; CEA, WTP of £0 per additional, e.g., treatment responder.

MDD

Treatment of MDD, minor/subthreshold depression, and depressive symptoms. Fifteen studies evaluated IMIs for MDD ($n = 8$) and depressive symptoms ($n = 5$), whereas two studies focused on depression onset and relapse prevention. The control conditions

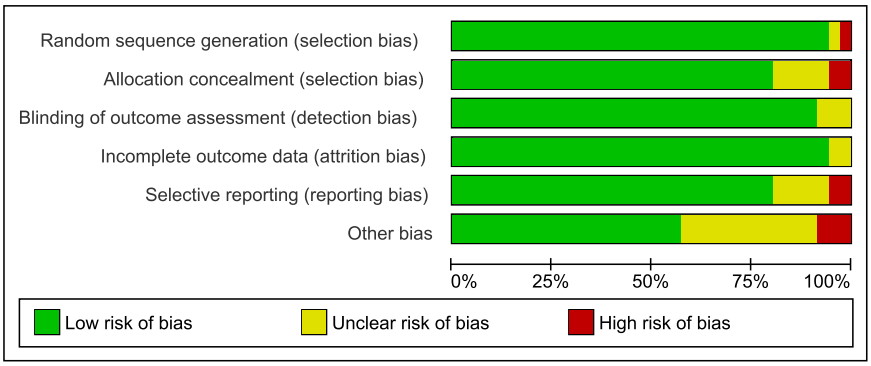


Fig. 2 Risk of bias assessment. The graph displays the authors' judgments on risk of bias of each included study, presented as percentage totals according to the Cochrane Collaborations tool.

consisted of alternative guidance formats: iPST, iPPI, iPCT, standard care, stepped care pathway, treatment as usual (TAU), WLC, and attention control (AC). Depressive symptom severity at baseline had no recognizable effect on cost-effectiveness.

One-third of the studies ($n = 5$) evaluated unguided IMIs based on CBT ($n = 4$) or positive psychology ($n = 1$[48]). As for unguided IMIs compared with TAU ($n = 3$), results from the CUA conducted from the healthcare perspective after 1–2 years did not suggest an economic merit[40,49] (at a WTP threshold of £30,000, the probability of cost-effectiveness varied: CUA = 4–38%). However, findings from the societal perspective suggested that one IMI[50] had an acceptable likelihood of being cost-effective (at WTP = 0, CEA = 70%; at WTP = £30,000; CUA = 55%). Compared with WLC or AC ($n = 2$), unguided IMIs from the societal perspective provided only little and unclear evidence for cost-effectiveness (at the WTP = 0, CEA = 20%[48]; CUA was not reported[41]).

Six of the 15 studies evaluated guided IMIs based on iCBT ($n = 4$) or iPST ($n = 2$). Two guided IMIs were compared with TAU and showed opposing results after 6–12 months. Findings from the societal perspective showed a moderate-to-acceptable likelihood of being cost-effective (at WTP = 0, CEA = 48[51]–62%[52]), one above[52] and one below[51] the proposed threshold of £30,000. From the employer's perspective, one IMI was the dominant treatment option (WTP = 0, CEA = 55%)[52].

Four guided[53–56] IMIs, compared with WLC, were considered cost-effective (<£30,000 per QALY gained, probabilities ranging from 55[53] to 98%[55]) from the societal and healthcare perspective. Results of the cost-effectiveness analyses were unclear[54] or showed a low likelihood of being cost-effective at a WTP of nil from a societal perspective (CEA = 30–38%[53]).

Two studies compared similarly effective guided to unguided IMIs after 12 months. In one study, from the societal perspective, both IMIs generated less costs than usual care and were judged cost-effective[57] (<£30,000 per QALY gained, probabilities were not reported). In the other study, from the NHS' perspective, the guided IMI resulted in more QALYs gained at lower costs than the unguided IMI (considered cost-effective, at WTP = £ 30,000, CUA = 55%[39]).

Prevention of MDD onset and relapse prevention. The remaining studies evaluating guided IMIs ($n = 2$) focused on the prevention[43] or relapse[44] of MDD in comparison with usual care. Findings from cost-effectiveness analyses employing a societal perspective suggested a moderate likelihood of them being cost-effective, with probabilities ranging from 38% to 40% at a WTP of nil. CUA showed a moderate (CUA = 40%[44]) to acceptable (CUA = 60%[43]; ICUR < £30,000 per QALY gained) likelihood of them being cost-effective. From the healthcare perspective, one IMI[43] showed a small likelihood of being cost-effective per depression-free year gained (WTP = 0, CEA = 17%) but was considered cost-effective when below the cost-utility threshold (at WTP = £30,000, CUA = 64%).

Anxiety disorders or symptoms. Eight studies evaluated guided ($n = 5$) and unguided ($n = 3$) IMIs for anxiety disorders based on CBT compared with TAU, AC, WLC, group-administered CBT (gCBT), or iMA. The included studies targeted panic disorder ($n = 1$), generalized anxiety disorder (GAD) ($n = 1$), health anxiety ($n = 2$), social anxiety ($n = 2$), any anxiety disorder ($n = 1$), and PTSD ($n = 1$).

Three studies comparing guided IMIs to AC or WLC in the short term (8–12 weeks) were judged cost-effective from the societal and healthcare perspectives (<£30,000, per QALY gained, probabilities >90%[46,58,59]). Cost-effectiveness analyses showed that the IMIs dominated the control group by generating less costs at higher effects from the societal perspective (at WTP = 0, CEA = 64[58]–95%[46]).

Two studies comparing guided IMIs with gCBT after 6 months to 4 years provided good evidence for their cost-effectiveness. The first IMI was cost-effective from the societal perspective in the short and long term (<£30,000 per QALY gained, CUA = 34[37]–79%[36]). Results of the cost-effectiveness analyses showed that the IMI produced less costs at higher effects (WTP = 0, CEA = 81%[36]) in the short term and increased costs with lower probability of being cost-effective in the long term (WTP = 0, CEA = 62%[37]). From a healthcare perspective, the same IMI was cost-effective based on a CMA (WTP = £30,000, CMA = 67%[38]). The second IMI was likewise cost-effective from the healthcare perspective, being the dominant treatment option (WTP = 0, CEA = 75%[45]).

By contrast, for two studies evaluating unguided IMIs, the results of the cost-utility analyses were considered cost-effective (yet no probabilities were reported), but the CEA did not support these findings. The first IMI[60] was compared with unguided iMA from a societal perspective, which resulted in higher costs per responder, showing low probabilities of being cost-effective (at WTP = 0, CEA = 8%), but being below the £30,000 threshold per QALY gained. The second IMI generated less costs per QALY gained than WLC from both healthcare and societal perspectives[61]. A third unguided study compared an unguided IMI (self-help app) targeting posttraumatic stress[62] with TAU from a healthcare perspective and showed a low probability of cost-effectiveness (≈27% at WTP = £30,000 per QALY gained).

OCD

Three studies evaluated guided IMIs for OCD based on CBT in comparison with either self-help book with guidance, WLC, AC, or a booster session. The evidence for cost-effectiveness was contradictory regarding QALYs and moderate regarding clinical outcomes because of heterogeneous control conditions.

From the societal and healthcare perspective, one IMI was cost-effective compared with AC being below the acceptable threshold per QALY gained (at WTP £30,000, CUA = 90–95%[63]). By contrast, the IMI was judged not cost-effective per additional remission in the short term (at WTP = 0, CEA = 0–15%) nor per relapse

Table 3. Risk of bias assessment.

Nr	Author (ref.)	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of outcome assessment (detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Other bias
1	Bolier et al.[48]	Low risk	Unclear risk	Low risk	Low risk	Low risk	Unclear risk
2	Buntrock et al.[43]	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
3	Gerhards et al.[50]	Unclear risk	Low risk	Low risk	Low risk	Low risk	Low risk
4	Phillips et al.[41]	Low risk	Low risk	Low risk	High risk	High risk	High risk
5	Titov et al.[56]	Low risk	Low risk	Low risk	Low risk	Low risk	High risk
6	Van Luenen et al.[55]	Low risk	Low risk	Unclear risk	Low risk	Low risk	Unclear risk
7	Brabyn et al.[39]	Low risk	High risk	Low risk	Low risk	Low risk	Unclear risk
8	Geraedts et al.[52]	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
9	Hollinghurst et al.[54]	Low risk	Low risk	Unclear risk	Low risk	Low risk	Unclear risk
10	Klein et al.[44]	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
11	Littlewood et al.[40]	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
12	Nobis et al.[51]	Low risk	Unclear risk	Unclear risk	Low risk	Low risk	Unclear risk
13	Romero-Sanchiz et al.[57]	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
14	Warmerdam et al.[53]	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
15	Yan et al.[49]	Low risk	Low risk	Low risk	Low risk	Low risk	Unclear risk
16	Bergström et al.[45]	Low risk	Unclear risk	Low risk	Unclear risk	High risk	Low risk
17	Dear et al.[59]	Low risk	Low risk	Low risk	Low risk	Unclear risk	Unclear risk
18	Nordgren et al.[46]	Low risk	Low risk	Low risk	Low risk	Unclear risk	Low risk
19	Hedman et al.[58]	Low risk	Low risk	Low risk	Low risk	Unclear risk	Unclear risk
20	Hedman et al.[60]	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
21	Hedman et al.[36]	Low risk	Low risk	Low risk	Low risk	Unclear risk	Low risk
22	Hedman et al.[37]	Low risk	Low risk	Low risk	Low risk	Unclear risk	Low risk
23	Alaoui et al.[38], SW	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
24	Powell et al.[61]	Low risk	Low risk	Low risk	Low risk	Low risk	Unclear risk
25	Andersson et al.[63]	Low risk	Low risk	Low risk	Low risk	Unclear risk	Low risk
26	Andersson et al.[64]	High risk	High risk	Low risk	Unclear risk	Low risk	Low risk
27	Lenhard et al.[65]	Low risk	Unclear risk	Low risk	Low risk	Low risk	Unclear risk
28	Lovell et al.[66]	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
29	Röhr et al.[62]	Low risk	Low risk	Low risk	Low risk	Low risk	Unclear risk
30	De Bruin et al.[67]	Low risk	Unclear risk	Low risk	Low risk	Low risk	Low risk
31	Thiart et al.[35]	Low risk	Low risk	Low risk	Low risk	Low risk	Unclear risk
32	Buntrock et al.[34]	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
33	Ebert et al.[32]	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
34	Kählke et al.[33]	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
35	Lindsäter et al.[68]	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
36	Van Spijker et al.[70]	Low risk	Low risk	Low risk	Low risk	Low risk	High risk

prevented after 2 years when a booster session was offered in a crossover design (at WTP = 0, CEA = 0–18%[64]).

Two studies compared IMIs with WLC after 3 months. From the societal and healthcare perspectives, one study did not report probabilities of cost-effectiveness nor ICUR[65], and the other was neither cost-effective compared with WLC (ICUR > 30,000 per QALY gained[66], CUA = 35–52%) nor more effective than guided self-help.

Other mental disorders. Most of the remaining five studies used CBT (guided, $n = 4$; unguided, $n = 1$), and only one intervention used iMA. The IMIs targeted insomnia, perceived stress or stress-

related disorders, or suicidal ideation and showed a moderate to high probability of cost-effectiveness.

IMIs targeting insomnia were cost-effective per QALY gained but unconvincing regarding cost-effectiveness analyses. One IMI was cost-effective compared with WLC and below the threshold per QALY gained (at WTP = £30,000[34], CUA = 99%) from the societal and healthcare perspectives. Cost-effectiveness analyses also showed a high probability of being cost-effective, dominating the WLC per additional treatment responder (CEA = 87%, employer's perspective[35]) or symptom-free status (CEA = 94%, societal perspective[34]), but generating higher costs from the healthcare perspective, leading to a low probability of cost-effectiveness (CEA = 6%[34]).

Another IMI[67] was compared with gCBT from a societal perspective. Both treatments showed similar effects, and the IMI led to a high probability of cost-savings while trading off health gains (at WTP = 0, CEA = 95%) but generating more QALYs (at WTP = £30.000, CUA = not reported).

IMIs targeting adjustment or exhaustion disorder, or perceived stress, were mostly cost-effective compared with WLC. Based on findings of the cost-utility analyses, two IMIs were below the threshold of £30.000, showing high probabilities of being cost-effective from the societal perspective (CUA = 75[68]–79%[33]). In addition, findings of the cost-effectiveness analyses showed that both IMIs dominated the WLC, yielding acceptable probabilities of cost-effectiveness at a WTP of nil from the employer's (CEA = 67%[69]) and societal (CEA = 70%[33]) perspectives, but not from the healthcare perspective (CEA = 12%[68]) where higher costs were generated.

The only unguided IMI[70] targeting suicidal ideation dominated the WLC, generating a high probability of being cost-effective at a WTP of nil from the societal perspective (CEA = 92%).

Workplace setting. Cost-benefit analyses evaluating costs relevant to the employer yielded a benefit-to-cost ratio (BCR) > 1 (1.6–3.1) and net-benefit greater zero (181–417), which indicates that guided IMIs were cost-effective when compared with TAU and WLC for the treatment of insomnia[35], elevated stress[69], and depression[52].

Guidance and comparators. The majority of studies evaluated guided IMIs ($n = 24$), which were mostly cost-effective, indicated by ICURs < £30,000/QALY gained, irrespective of the types of control conditions. However, unguided IMIs ($n = 11$) showed little evidence of cost-effectiveness.

DISCUSSION

This review presents a comprehensive overview of trial-based economic evaluations providing evidence regarding the cost-effectiveness of IMIs for the prevention and treatment of MDs and symptoms. This review identified 32 studies applying societal ($n = 24$), healthcare ($n = 15$), and employer's perspectives ($n = 3$) in 65 full economic evaluations (CBA, $n = 3$; CEA, $n = 31$; CMA, $n = 1$; CUA, $n = 30$).

In half of the CEAs ($N = 14$; MDD, $n = 3$; anxiety, $n = 5$; stress, $n = 3$; sleep $n = 2$; suicidal ideation, $n = 1$), the IMI was the dominant treatment option, which means that more health effects were generated at lower costs in comparison with control conditions. Of these, two did not report a WTP and five showed a high probability (≥80%) of being more cost-effective than control conditions at a WTP of nil. For all CEAs, the range of probability at WTP of nil varied from 0 to 95%. Regarding cost-utility, most interventions were cost-effective, being either dominant ($n = 13$) and/or below the WTP threshold of £30,000 per QALY gained ($n = 26$) compared with any control condition and often regardless of the perspectives taken. By applying the criterion that an IMI showed at least an 80% probability of cost-effectiveness at WTP of £30,000 compared with a control condition (if reported), 11 IMIs were judged to be cost-effective. Cost-benefit analyses from the employer's perspective ($n = 3$) yielded positive net benefits representing the money gained after costs were recovered. In addition, the overall quality of studies (CHEC) was good ($n = 30$), only a few were excellent ($n = 3$) or average ($n = 3$). Reasons for a low rating were no discussion of generalizability, short time horizon, or lack of sensitivity analyses. Regarding RoB, most studies showed good quality ($n = 22$), and only few studies ($n = 6$) showed at least one item at high risk of bias.

Our findings expand and strengthen the evidence base for the cost-effectiveness of IMIs. First, our findings support the evidence of cost-effectiveness of guided IMIs for depression and anxiety[24,25,27–29]. Second, our review includes new evidence related to under-researched disorders such as OCD ($n = 4$), PTSD ($n = 1$), stress ($n = 3$), and sleep ($n = 2$). However, given the limited number of studies, more evidence is needed.

The strength of this review is related to the comprehensive and systematic search strategy in several electronic databases for common MDs and problems, and the resulting health-economic comparisons. The quality of studies was assessed on the methodology of cost-effectiveness analyses and RoB. To further improve comparability and clarity, economic outcomes were converted to Pound Sterling for the reference year 2020 and mapped to the quadrant of the cost-effectiveness plane in which the mean ICER fell (as far as reported in the primary studies). Likewise, unified thresholds and transparent criteria proposed by the authors were used.

However, the comparability of evidence across the studies was hampered by the high heterogeneity stemming from different study designs, methods, study populations, outcome measures, time horizons, comparators, economic perspectives, cost items, and their evaluation. As a case in point, the operationalization of societal costs and intervention costs varied widely. The costs of development and maintenance of the IMIs were often not included or incompletely reported, leading to a possible underestimation of intervention costs. Half of the studies ($n = 16$) did not report intervention costs or only valued the time for the therapist needed to support the participants.

Another limitation is the lack of interpretability regarding cost-effectiveness, as the WTP for diagnosis-specific measures (e.g., symptom-free, reliable change) is unknown and the WTP threshold for QALYs is somewhat arbitrary, as universally accepted thresholds are unavailable[71]. For healthcare decision-making, several countries compared ICER to a reference value (generic cost-effectiveness threshold) that represents the maximum cost the health system is willing to pay for a health outcome. These generic thresholds vary largely depending on the methods (e.g., per capita income, benchmarking interventions, and leagues tables: ranking the ICERs of interventions given a specific budget) and setting[71]. An international survey assessing the individual WTP for one additional QALY gained showed that the thresholds vary between countries (e.g., Taiwan 2.14 times the UK's per QALY gained)[72]. Consequently, higher thresholds lead to interventions being adopted earlier than in countries with lower thresholds. Beyond the narrow cost-effectiveness arguments, other criteria of health technology assessment should also be considered for decision-making purposes (e.g., disease burden, prognosis, medical ethics, access, equity, feasibility of implementation and scale-up of the interventions, and acceptability of the intervention by its intended recipients)[73]. Furthermore, most health-economic evaluations alongside randomized controlled trials (RCTs) are not powered to detect differences in costs nor QALYs. This might result in non-significant differences in costs and QALYs, which can lead to wider uncertainty intervals surrounding the ICER estimates[74]. Moreover, some studies ($n = 3$) only collected data over a short period of the study duration and annualized effects and costs. In addition, in some studies ($n = 6$), the uncertainty surrounding the ICER point estimates was not clear because

neither the CEA plane nor the cost-effectiveness acceptability curve where reported. As all studies were conducted in Western countries, especially in the NW Europe, the generalizability of results is restricted to these regions. In this regard, selection bias could have been introduced, as only studies published in German and English were included.

The results may lead to several clinical implications. The review could be important for decision-makers when allocating scant resources to meet the demands for the many in need of sustainable healthcare. With the increasing use of economic data in decision-making in public mental health and the increasing societal and economic burden of MDs, consideration of the cost-effectiveness of psychological preventive interventions and treatments is becoming increasingly important. IMIs might be an important way forward. Moreover, since the COVID-19 pandemic, increasing numbers of patients and health services had to shift toward IMIs for the receipt and delivery of mental healthcare. Thus, this may have paved the way for scaled-up uptake of IMIs.

Despite the high heterogeneity stemming from intervention types and comparators of the included studies, some promising trends toward specific mental health targets were seen. Recommendations for policy makers and relevant stakeholders can be made, relating to existing NHS guidelines[75] for the application of low-intensity psychosocial interventions in depression and anxiety. Based on our results, guided IMIs for MDD and anxiety disorders should be offered as treatment option. The evidence regarding the cost-effectiveness of under-researched disorders (e.g., OCD, sleep, and stress) and of unguided interventions is limited, and offering such interventions should rely on case-by-case decisions. However, unguided IMIs are scalable and easy to implement, showing a high potential to make an impact at a population level.

Besides these recommendations related to financial aspects, the implementation setting, target population, symptom severity and disorders should be considered. In addition, knowledge about diverse stakeholders' views and values relevant to priority setting enables decision-makers to make better-informed decisions and appropriate judgments about allocation of scant resources.

In practice, most healthcare providers are receptive to the advantages of IMIs as part of their treatment. However, IMIs should meet the criteria of government reimbursement mechanisms, like the National Institute for Health and Clinical Excellence's (NICE) in the UK or the one for digital health applications in medical and psychotherapeutic care in Germany, to become sustainable. Such criteria include evidence on effectiveness, interoperability, safety, and data security[76].

Following this, we provide several recommendations for future research. First, various anxiety disorders such as panic disorder, GAD, and social anxiety were underrepresented, and disorders such as specific phobias were not found for this review. Moreover, studies were only conducted in resource-rich high-income countries. Hence, we recommend focusing on under-researched disorders and conducting research in low- and middle-income countries.

Second, we recommend publishing study protocols that adhere to economic evaluation guidelines (ISPOR[77] and CHEERS[78]) and quality checklists (Drummond[31] and CHEC[79]), thereby minimizing biases and improving study quality (e.g., reporting of uncertainty, sensitivity analysis and combined reporting of disease-specific and generic health outcomes to facilitate comparability, and interpretation for decision-making).

Third, the cost-effectiveness of IMIs for MDs and symptoms was frequently based on short term findings (6–16 weeks, $n = 13$), whereas the remaining studies reported findings based on moderate (6–12 months, $n = 14$) to long follow-up periods (2–4 years, $n = 3$). We recommend conducting economic evaluations over longer follow-up periods to better capture longer-term productivity losses and gains, especially in preventive interventions in remittent disorders, such as anxiety disorders.

Fourth, more research is needed on IMIs compared with active control condition across all disorders to establish the cost-effectiveness of IMIs as possible alternative to face-to-face treatments.

Fifth, studies are needed to carefully choose the perspectives taken depending on the decision maker, target population, disorder, or setting. For employers, productivity losses are most important, whereas from a healthcare system's perspective, a high healthcare coverage for people affected by disorders is prioritized.

Finally, the acceptability of an IMI among patients and relevant stakeholders is worth investigating to provide more insights pertinent for the implementation, uptake, and use thereof.

In conclusion, this systematic review provides an overview of economic evaluations of internet-based interventions for the treatment and prevention of MDs. Guided iCBTs for anxiety disorders and MDD showed a high probability of being cost-effective. IMIs for insomnia, suicidal ideation, and stress had the potential of being cost-effective, whereas the evidence base for the cost-effectiveness of IMIs in OCD was not very firm. Although many studies were identified, more robust conclusions about the cost-effectiveness of IMIs could not be reached given the high heterogeneity across the studies with regard to methodologies, interventions, and comparators in a range of disorders and symptoms among various populations and age groups. More cost-effectiveness research is warranted in unguided and preventive IMIs that are proven to be effective, specifically in under-researched disorders and symptoms and preferably over longer time horizons. From a methodological perspective, future studies should more stringently adhere to existing health-economic guidelines to increase comparability and enhance their value for decision-making purposes in healthcare.

METHODS

The guidelines of Preferred Reporting Items for Systematic Reviews and Meta-Analyses[80] and preparation for systematic reviews of economic evaluations[81] were followed. This systematic review was registered in the international prospective register of systematic reviews, PROSPERO (CRD42018093808[82]).

Search strategy

An extensive literature search was conducted, using the following electronic databases: MEDLINE, PsycINFO, Cochrane Central Register of Controlled Trials (CENTRAL), PSYNDEX, and National Health Service (NHS) Economic Evaluations Database. Relevant articles published before 10/05/2021 were identified using standardized subject terms. A search strategy consisting of four main categories was applied for each database selecting articles referring to (1) intervention, treatment, prevention, or psychotherapy; (2) MDs, (3) internet, online, or mobile-based; and (4) economic evaluation (Supplementary Table 2).

Eligibility criteria

Studies were eligible for inclusion if they met the following inclusion criteria:

Population: participants regardless of age with a diagnosis of MD or symptoms such as MDD, dysthymia, bipolar disorder, social phobia, panic disorder, GAD, PTSD, OCD, specific phobia, and separation anxiety, sleep disorders, or transdiagnostic key symptoms such as suicidal thoughts, and psychological distress, all of which were required to be assessed with validated self-report questionnaires or being based on diagnostic interviews.

Intervention: psychological interventions that are provided in an online setting, defined as internet-, online-, web-, or mobile-based

and grounded in CBT, interpersonal therapy, problem-solving therapy, positive psychology intervention, psychodynamic therapies, behavior therapy or behavior modification, systemic therapies, third-wave cognitive behavioral therapies, humanistic therapies, or integrative therapies. Internet-based interventions can be "guided", offering patients human support by a psychotherapist via email or chat or automated feedback delivery, or "unguided", only offering self-help interventions without any additional human support.

Comparator: included one of the following control groups: another psychological intervention, TAU, WLC, or AC group.

Outcome measures: reported economic evaluation estimates based on CEA, CUA, CBA, and CMA of a full economic evaluation, which means that the study compared both costs and effects (e.g., QALYs, treatment response, relapse avoided, and remission) of two or more alternatives.

Study types: RCTs, full texts are accessible as peer-reviewed papers, in English or German.

Studies were excluded if the intervention was not delivered online. IMIs were excluded when provided in combination with a face-to-face or video-based sessions delivered by a therapist (i.e., blended intervention). Studies were excluded if they did not report a meaningful outcome measure for economic evaluation (e.g., point improvement on an ordinal scale). Health-economic modeling studies were excluded because of methodological differences compared with trial-based economic evaluations (e.g., not directly based on observational data) limiting internal validity of the review. Conference abstracts, protocol papers, non-peer-reviewed papers, cost of illness, observational studies, cohort studies, case studies, pilot studies, and feasibility studies were also excluded.

Study selection and extraction

First, titles and abstracts of the identified articles were screened. Then, studies were evaluated whether they met the criteria in full text by two independent researchers, F.K. and C.B. Disagreement was discussed and/or a third reviewer (D.D.E.) consulted. Interrater agreement (Cohen's kappa) of the two reviewers was examined.

Data of eligible studies were extracted using the Consolidated Health Economic Evaluation Reporting Standards Checklist[78]: (1) characteristics of participants (setting, age, sex, and screened symptoms/diagnosis), (2) study design (sample size, trial arms, and assessment points), (3) intervention (psychological approach, guidance, and length of intervention), (4) economic outcome measures, (5) type of economic evaluation, (6) characteristics of derived costs (cost categories, cost data sources, price year, currency, and mean incremental costs), (7) perspective of economic evaluation, and (8) cost-effectiveness estimates, such as incremental costs (i.e., cost difference between IMI and comparator), incremental effects, ICER, and ICER acceptability for various WTP levels.

Summary measures

Only base-cases analyses adhering to the intention-to-treat (ITT) principle were reported. Cost-effectiveness is ascertained when an intervention dominates the alternative, so it is both more effective and less costly or provides a greater outcome at higher costs that the society is willing to pay for[31]. In practice, interventions often show greater effects for higher costs. The efficacy of interventions is one of the indicators for their cost-effectiveness, as it represents the denominator of the ICER. Consequently, most often, the investment required for obtaining a favorable health outcome decreases with increasing effectiveness. Therefore, more effective treatments have a higher probability of being cost-effective. The relative effectiveness of an intervention is further influenced by its comparator, with smaller incremental effects in active comparator interventions to larger incremental effects in passive control groups[4]. Similarly, the level of therapist-led guidance in IMIs induces some effect moderation because it adds costs to an IMI, but may also enhance its effectiveness[4,83]. This is important when making conclusions about incremental cost-effectiveness. In this review, IMIs were judged to be cost-effective when:

- the IMI was dominant, i.e., the IMI's effect was better, and its costs were lower than those of the comparator;
- the costs per QALY was below the WTP of £30,000 as suggested by the NICE[84];
- studies using disease-specific clinical outcome such as treatment response, reliable change, were judged to be cost-effective when the probability of cost-effectiveness at a WTP of £0 was 80% or higher, which provides a high level of certainty for decision-making.

This means that the intervention is estimated to be more effective and costly in 80% of the cases. This criterion can be seen as conservative, as most interventions show higher effects at higher costs than alternative interventions. Again, as no thresholds for the WTP of these units of effect exist, applicable studies should be judged individually by decision-makers.

To facilitate comparison between countries, all national currencies were converted to Pound Sterling for the price year 2020[85]. First, the currency of the study was indexed to a 2020 equivalent by country-specific gross domestic product inflators (e.g., euro area 19) and then converted to Pound Sterling (£) using purchasing power parities[86].

Quality assessment

The quality of health-economic evaluations was assessed using the CHEC[79]. This 20-item checklist was developed to evaluate the methodological quality (internal and external validity) of economic evaluations. The total score is expressed as the percentage of the maximum score for each study. A summary quality score was calculated[24] (percentage of criteria met by each study [range: 0–100%]) based on a scoring of "yes" (= 1), "suboptimal" (= 0.5), "no" (= 0), not applicable (NA)[24]. The following quality categories were used: excellent (100–95%), good (75–94%), average (50–74%), and poor (<50%).

In addition, Cochrane Collaboration's tool for assessing RoB was used[87] to determine selection, performance, detection, attrition, reporting, and other bias in research studies. Each item was rated as high, low, unclear RoB, or NA. Performance bias was not assessed, as participants and personnel cannot be blinded due to the nature of IMIs. Furthermore, detection bias was always rated as low, as IMIs commonly rely on self-report instruments. Incomplete outcome data were rated as low risk when data analysis was conducted in accordance with the ITT principle. RoB was converted to the Agency for Healthcare Research and Quality[88] standards (i.e., good, fair, or poor quality). RoB and CHEC were rated independently by F.K. and C.B. Disagreement was discussed or resolved by a third reviewer (D.D.E.).

Reporting summary

Further information on research design is available in the Nature Research Reporting Summary linked to this article.

Received: 21 February 2022; Accepted: 3 October 2022;
Published online: 23 November 2022

REFERENCES

1. Kessler, R. C. et al. The global burden of mental disorders: an update from the WHO World Mental Health (WMH) surveys. *Epidemiol. Psichiatr. Soc.* **18**, 23–33 (2009).
2. Steel, Z. et al. The global prevalence of common mental disorders: a systematic review and meta-analysis 1980-2013. *Int. J. Epidemiol.* **43**, 476–493 (2014).

3. Walker, E. R., McGee, R. E. & Druss, B. G. Mortality in mental disorders and global disease burden implications a systematic review and meta-analysis. *JAMA Psychiatry* **72**, 334–341 (2015).
4. Andrews, G. et al. Computer therapy for the anxiety and depression disorders is effective, acceptable and practical health care: an updated meta-analysis. *J. Anxiety Disord.* **55**, 70–78 (2018).
5. Mack, S. et al. Functional disability and quality of life decrements in mental disorders: results from the Mental Health Module of the German Health Interview and Examination Survey for Adults (DEGS1-MH). *Eur. Psychiatry* **30**, 793–800 (2015).
6. Scott, K. M. et al. Association of mental disorders with subsequent chronic physical conditions. *JAMA Psychiatry* **73**, 150–158 (2016).
7. Baglioni, C. et al. Sleep and mental disorders: a meta-analysis of polysomnographic research. *Psychol. Bull.* **142**, 969–990 (2016).
8. GBD 2015 DALYs and HALE Collaborators. Global, Regional, and National Disability-adjusted Life Years (Dalys) for 315 diseases and injuries and healthy life expectancy (Hale), 1990-2015: a systematic. *Lancet* **388**, 1603–1658 (2016).
9. Vigo, D., Thornicroft, G. & Atun, R. Estimating the true global burden of mental illness. *Lancet Psychiatry* **3**, 171–178 (2016).
10. Bloom, D. E. et al. The global economic burden of non-communicable diseases. http://www3.weforum.org/docs/WEF_Harvard_HE_GlobalEconomicBurden NonCommunicableDiseases_2011.pdf (2011).
11. Gustavsson, A. et al. Cost of disorders of the brain in Europe 2010. *Eur. Neuropsychopharmacol.* **21**, 718–779 (2011).
12. Cuijpers, P. et al. The efficacy of psychotherapy and pharmacotherapy in treating depressive and anxiety disorders: a meta-analysis of direct comparisons. *World Psychiatry* **12**, 137–148 (2013).
13. Kazdin, A. E. Addressing the treatment gap: a key challenge for extending evidence-based psychosocial interventions. *Behav. Res. Ther.* **88**, 7–18 (2017).
14. De Girolamo, G., Dagani, J., Purcell, R., Cocchi, A. & McGorry, P. D. Age of onset of mental disorders and use of mental health services: needs, opportunities and obstacles. *Epidemiol. Psychiatr. Sci.* **21**, 47–57 (2012).
15. Andrade, L. H. et al. Barriers to mental health treatment: results from the WHO World Mental Health surveys. *Psychol. Med.* **44**, 1303–1317 (2014).
16. Griffiths, F., Lindenmeyer, A., Powell, J., Lowe, P. & Thorogood, M. Why are health care interventions delivered over the internet? A systematic review of the published literature. *J. Med. Internet Res.* **8**, 1–16 (2006).
17. Ebert, D. D., Cuijpers, P., Muñoz, R. F. & Baumeister, H. Prevention of mental health disorders using internet- and mobile-based interventions: a narrative review and recommendations for future research. *Front. Psychiatry* **8**, 1–16 (2017).
18. Sander, L. et al. Effectiveness of internet-based interventions for the prevention of mental disorders: a systematic review and meta-analysis. *JMIR Ment. Heal* **3**, 1–20 (2016).
19. Rosenbaum, S., Newby, J. M., Steel, Z., Andrews, G. & Ward, P. B. Online physical activity interventions for mental disorders: a systematic review. *Internet Inter.* **2**, 214–220 (2015).
20. Stratton, E. et al. Effectiveness of eHealth interventions for reducing mental health conditions in employees: a systematic review and meta-analysis. *PLoS ONE* **12**, 1–23 (2017).
21. Gomes, M., Murray, E. & Raftery, J. Economic evaluation of digital health interventions: methodological issues and recommendations for practice. *Pharmacoeconomics* **40**, 367–378 (2022).
22. Hedman, E., Ljótsson, B. & Lindefors, N. Cognitive behavior therapy via the internet: a systematic review of applications, clinical efficacy and cost-effectiveness. *Expert Rev. Pharmacoecon. Outcomes Res.* **12**, 745–764 (2012).
23. Arnberg, F. K., Linton, S. J., Hultcrantz, M., Heintz, E. & Jonsson, U. Internet-delivered psychological treatments for mood and anxiety disorders: a systematic review of their efficacy, safety, and cost-effectiveness. *PLoS ONE* **9**, 1–13 (2014).
24. Ophuis, R. R. H. et al. Cost-effectiveness of interventions for treating anxiety disorders: a systematic review. *J. Affect. Disord.* **210**, 1–13 (2017).
25. Paganini, S., Teigelkötter, W., Buntrock, C. & Baumeister, H. Economic evaluations of internet- and mobile-based interventions for the treatment and prevention of depression: a systematic review. *J. Affect. Disord.* **225**, 733–755 (2018).
26. Conejo-Cerón, S. et al. Health-economic evaluation of psychological interventions for depression prevention: systematic review. *Clin. Psychol. Rev.* **88**, 102064 (2021).
27. Kolovos, S. et al. Cost effectiveness of guided Internet-based interventions for depression in comparison with control conditions: an individual–participant data meta-analysis. *Depress Anxiety* **35**, 209–219 (2018).
28. Donker, T. et al. Economic evaluations of internet interventions for mental health: a systematic review. *Psychol. Med.* **45**, 3357–3376 (2015).
29. Mitchell, L., Joshi, U., Patel, V., Lu, C. & Naslund, J. A. Economic evaluations of internet-based psychological interventions for anxiety disorders and depression: a systematic review. *J. Affect. Disord.* **284**, 157–182 (2021).
30. Karyotaki, E., Tordrup, D., Buntrock, C., Bertollini, R. & Cuijpers, P. Economic evidence for the clinical management of major depressive disorder: a systematic review and quality appraisal of economic evaluations alongside randomised controlled trials. *Epidemiol. Psychiatr. Sci.* **26**, 501–516 (2017).
31. Drummond, M., Sculpher, M. J., Claxton, K., Stoddart, G. L. & Torrance, G. W. *Methods for the Economic Evaluation of Health Care Programmes* (Oxford University Press, 2015).
32. Ebert, D. D. et al. A health economic outcome evaluation of an internet-based mobile-supported stress management intervention for employees. *Scand. J. Work. Environ. Health* **44**, 171–182 (2018).
33. Kählke, F. et al. Economic evaluation of an internet-based stress management intervention alongside a randomized controlled trial. *JMIR Ment. Heal.* **6**, 1–13 (2019).
34. Buntrock, C. et al. Guided internet-based cognitive behavioral therapy for insomnia: health-economic evaluation from the societal and public health care perspective alongside a randomized controlled trial. *J. Med. Internet Res.* **23**, 1–15 (2021).
35. Thiart, H. et al. Internet-based cognitive behavioral therapy for insomnia: a health economic evaluation. *Sleep* **39**, 1769–1778 (2016).
36. Hedman, E. et al. Cost-effectiveness of internet-based cognitive behavior therapy vs. cognitive behavioral group therapy for social anxiety disorder: results from a randomized controlled trial. *Behav. Res. Ther.* **49**, 729–736 (2011).
37. Hedman, E. et al. Clinical effectiveness and cost-effectiveness of internet- vs. group-based cognitive behavior therapy for social anxiety disorder: 4-year follow-up of a randomized trial. *Behav. Res. Ther.* **59**, 20–29 (2014).
38. El Alaoui, S., Hedman-Lagerlof, E., Ljotsson, B. & Lindefors, N. Does internet-based cognitive behaviour therapy reduce healthcare costs and resource use in treatment of social anxiety disorder? A cost-minimisation analysis conducted alongside a randomised controlled trial. *BMJ Open* **7**, 1–9 (2017).
39. Brabyn, S. et al. The second Randomised Evaluation of the Effectiveness, cost-effectiveness and Acceptability of Computerised Therapy (REEACT-2) trial: does the provision of telephone support enhance the effectiveness of computer-delivered cognitive behaviour therapy? A randomised controlled trial. *Health Technol. Assess.* **20**, 1–64 (2016).
40. Littlewood, E. et al. A randomised controlled trial of computerised cognitive behaviour therapy for the treatment of depression in primary care: the Randomised Evaluation of the Effectiveness and Acceptability of Computerised Therapy (REEACT) trial. *Health Technol. Assess.* **19**, xxi–171 (2015).
41. Phillips, R. et al. Randomized controlled trial of computerized cognitive behavioural therapy for depressive symptoms: effectiveness and costs of a workplace intervention. *Psychol. Med.* **44**, 741–752 (2014).
42. Rantz, M. et al. Randomized trial of intelligent sensor system for early illness alerts in senior housing. *J. Am. Med. Dir. Assoc.* **18**, 860–870 (2017).
43. Buntrock, C. et al. Preventing depression in adults with subthreshold depression: health-economic evaluation alongside a pragmatic randomized controlled trial of a web-based intervention corresponding author. *J. Med. Internet Res.* **19**, 1–16 (2017).
44. Klein, N. S. et al. Economic evaluation of an internet-based preventive cognitive therapy with minimal therapist support for recurrent depression: randomized controlled trial. *J. Med. Internet Res.* **20**, 1–14 (2018).
45. Bergstrom, J. et al. Internet-versus group-administered cognitive behaviour therapy for panic disorder in a psychiatric setting: a randomised trial. *BMC Psychiatry* **10**, 1–10 (2010).
46. Nordgren, L. B. et al. Effectiveness and cost-effectiveness of individually tailored Internet-delivered cognitive behavior therapy for anxiety disorders in a primary care population: a randomized controlled trial. *Behav. Res Ther.* **59**, 1–11 (2014).
47. Landis, J. R. & Koch, G. G. The measurement of observer agreement for categorical data. *Biometrics* **33**, 159–174 (1977).
48. Bolier, L. et al. Cost-effectiveness of online positive psychology: randomized controlled trial. *J. Posit. Psychol.* **9**, 460–471 (2014).
49. Yan, C., Rittenbach, K., Souri, S. & Silverstone, P. H. Cost-effectiveness analysis of a randomized study of depression treatment options in primary care suggests stepped-care treatment may have economic benefits. *BMC Psychiatry* **19**, 1–13 (2019).
50. Gerhards, S. A. H. et al. Economic evaluation of online computerised cognitive-behavioural therapy without support for depression in primary care: randomised trial. *Br. J. psychiatry* **196**, 310–318 (2010).
51. Nobis, S. et al. Web-based intervention for depressive symptoms in adults with types 1 and 2 diabetes mellitus: a health economic evaluation. *Br. J. Psychiatry* **212**, 199–206 (2018).
52. Geraedts, A. S. et al. Economic evaluation of a web-based guided self-help intervention for employees with depressive symptoms: results of a randomized controlled trial. *J. Occup. Environ. Med.* **57**, 666–675 (2015).
53. Warmerdam, L., Smit, F., van Straten, A., Riper, H. & Cuijpers, P. Cost-utility and cost-effectiveness of Internet-based treatment for adults with depressive symptoms: randomized trial. *J. Med. Internet Res.* **12**, 40–50 (2010).
54. Hollinghurst, S. et al. Cost-effectiveness of therapist-delivered online cognitive-behavioural therapy for depression: randomised controlled trial. *Br. J. Psychiatry* **197**, 297–304 (2010).

55. van Luenen, S., Kraaij, V., Garnefski, N., Spinhoven, P. & van den Akker-van Marle, M. E. Cost-utility of a guided Internet-based intervention in comparison with attention only for people with HIV and depressive symptoms: a randomized controlled trial. *J. Psychosom. Res.* **118**, 34–40 (2019).
56. Titov, N. et al. Clinical and cost-effectiveness of therapist-guided internet-delivered cognitive behavior therapy for older adults with symptoms of anxiety: a randomized controlled trial (Provisional abstract). *Behav. Ther.* **46**, 206–217 (2015).
57. Romero-Sanchiz, P. et al. Economic evaluation of a guided and unguided internet-based CBT intervention for major depression: results from a multicenter, three-armed randomized controlled trial conducted in primary care. *PLoS ONE* **12**, 1–15 (2017).
58. Hedman, E. et al. Cost-effectiveness and long-term effectiveness of internet-based cognitive behaviour therapy for severe health anxiety. *Psychol. Med.* **43**, 363–374 (2013).
59. Dear, B. F. et al. Clinical and cost-effectiveness of therapist-guided internet-delivered cognitive behavior therapy for older adults with symptoms of anxiety: a randomized controlled trial (Provisional abstract). *Behav. Ther.* **46**, 206–217 (2015).
60. Hedman, E., Andersson, E., Ljotsson, B., Axelsson, E. & Lekander, M. Cost effectiveness of internet-based cognitive behaviour therapy and behavioural stress management for severe health anxiety. *BMJ Open* **6**, 1–8 (2016).
61. Powell, J. et al. Effectiveness and cost-effectiveness of a self-guided internet intervention for social anxiety symptoms in a general population sample: randomized controlled trial. *J. Med. Internet Res.* **22**, e16804 (2020).
62. Rohr, S. et al. A self-help app for Syrian refugees with posttraumatic stress (Sanadak): randomized controlled trial. *JMIR mHealth uHealth* **9**, e24807 (2021).
63. Andersson, E. et al. Cost-effectiveness of internet-based cognitive behavior therapy for obsessive-compulsive disorder: results from a randomized controlled trial. *J. Obsessive. Compuls. Relat. Disord.* **4**, 47–53 (2015).
64. Andersson, E. et al. Cost-effectiveness of an internet-based booster program for patients with obsessive-compulsive disorder: results from a randomized controlled trial (Provisional abstract). *J. Obsessive. Compuls. Relat. Disord.* **4**, 14–19 (2015).
65. Lenhard, F. et al. Cost-effectiveness of therapist-guided internet-delivered cognitive behaviour therapy for paediatric obsessive-compulsive disorder: results from a randomised controlled trial. *BMJ Open* **7**, e015246 (2017).
66. Lovell, K. et al. Clinical effectiveness, cost-effectiveness and acceptability of low-intensity interventions in the management of obsessive-compulsive disorder: the Obsessive-Compulsive Treatment Efficacy randomised controlled Trial (OCTET). *Health Technol. Assess.* **21**, 1–132 (2017).
67. De Bruin, E. J. et al. Cost-effectiveness of group and internet cognitive behavioral therapy for insomnia in adolescents: results from a randomized controlled trial. *Sleep* **39**, 1571–1581 (2016).
68. Lindsäter, E. et al. Cost-effectiveness of therapist-guided internet-based cognitive behavioral therapy for stress-related disorders: secondary analysis of a randomized controlled trial. *J. Med. Internet Res.* **21**, e14675 (2019).
69. Ebert, D. D. et al. A health economic outcome evaluation of an internet-based mobile-supported stress management intervention for employees. *Scand. J. Work. Environ. Heal.* **44**, 171–182 (2018).
70. van Spijker, B. A. J. et al. Reducing suicidal ideation: cost-effectiveness analysis of a randomized controlled trial of unguided web-based self-help. *J. Med. Internet Res.* **14**, e141 (2012).
71. McDougall, J. A., Furnback, W. E., Wang, B. C. M. & Mahlich, J. Understanding the global measurement of willingness to pay in health. *J. Mark. Access Heal. Policy* **8**, 1717030 (2020).
72. Shiroiwa, T. et al. International survey on willingness-to-pay (WTP) for one additional QALY gained: what is the threshold of cost effectiveness? *Health Econ.* **19**, 422–437 (2010).
73. Kan, K. et al. More than cost-effectiveness? Applying a second-stage filter to improve policy decision making. *Heal. Expect.* **24**, 1413–1423 (2021).
74. Fenwick, E., O'Brien, B. & Briggs, A. Cost-effectiveness acceptability curves: facts, fallacies and frequently asked questions. *Health Econ.* **13**, 405–415 (2004).
75. Kendrick, T. et al. Management of depression in adults: summary of updated NICE guidance. *BMJ* **378**, o1557 (2022).
76. Gerlinger, G., Mangiapane, N. & Sander, J. Digital health applications (DiGA) in medical and psychotherapeutic care. Opportunities and challenges from the perspective of the healthcare providers. *Bundesgesundheitsblatt Gesundheitsforsch Gesundheitsschutz* **64**, 1213–1219 (2021).
77. Ramsey, S. D. et al. Cost-effectiveness analysis alongside clinical trials II—an ISPOR Good Research Practices Task Force Report. *Value Heal* **18**, 161–172 (2015).
78. Husereau, D. et al. Consolidated Health Economic Evaluation Reporting Standards (CHEERS) statement. *Eur. J. Heal. Econ.* **14**, 367–372 (2013).
79. Thielen, F. W. et al. How to prepare a systematic review of economic evaluations for clinical practice guidelines: database selection and search strategy development (part 2/3). *Expert Rev. Pharmacoecon. Outcomes Res.* **16**, 705–721 (2016).
80. Page, M. J. et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. *Syst. Rev.* **10**, 1–11 (2021).
81. van Mastrigt, G. A. P. G. et al. How to prepare a systematic review of economic evaluations for informing evidence-based healthcare decisions: a five-step approach (part 1/3). *Expert Rev. Pharmacoecon. Outcomes Res* **16**, 689–704 (2016).
82. PROSPERO Registry. https://www.crd.york.ac.uk/PROSPERO/display_record.php?RecordID=93808 (2018).
83. Karyotaki, E. et al. Is self-guided internet-based cognitive behavioural therapy (iCBT) harmful? An individual participant data meta-analysis. *Psychol. Med.* **48**, 2456–2466 (2018).
84. McCabe, C., Claxton, K. & Culyer, A. J. The NICE cost-effectiveness threshold: what it is and what that means. *Pharmacoeconomics* **26**, 733–744 (2008).
85. Organisation for Economic Co-operation and Development (OECD). PPP and exchanges rates. https://data.oecd.org/conversion/purchasing.power-parties-ppp.htm (2018).
86. Tate, D. F., Finkelstein, E. A., Khavjou, O. & Gustafson, A. Cost effectiveness of internet interventions: review and recommendations. *Ann. Behav. Med.* **38**, 40–45 (2009).
87. Higgins, J. P. T. & Altman, D. G. Assessing risk of bias in included studies. In *Cochrane Handbook for Systematic Reviews of Interventions: Cochrane Book Series (*eds. Higgins, J. P. T. & Green, S.) 187–241 (WILEY, 2008). https://doi.org/10.1002/9780470712184.ch8.
88. Viswanathan, M. et al. Recommendations for assessing the risk of bias in systematic reviews of health-care interventions. *J. Clin. Epidemiol.* **97**, 26–34 (2018).

AUTHOR CONTRIBUTIONS

F.K., C.B., and D.D.E. were involved in the concept and design of the study. F.K. and C.B. made major contributions to data extraction. F.K., C.B., and F.S. discussed the analysis and interpretation of the data. F.K. wrote the first draft of the manuscript which was critically revised by C.B., F.S., and D.D.E. All authors contributed to and have approved the final manuscript.

FUNDING

Open Access funding enabled and organized by Projekt DEAL.

COMPETING INTERESTS

D.D.E. has served as a consultant to/on the scientific advisory boards of Sanofi, Novartis, Minddistrict, Lantern, Schoen Kliniken, Ideamed and German health insurance companies (BARMER, Techniker Krankenkasse) and a number of federal chambers for psychotherapy. He is also stakeholder in the Institute for health training online (formerly GET.ON, now HelloBetter), which aims to implement scientific findings related to digital health interventions into routine care. The other authors C.B., F.K., and F.S. declare no competing interests.

ADDITIONAL INFORMATION

Supplementary information The online version contains supplementary material available at https://doi.org/10.1038/s41746-022-00702-w.

Correspondence and requests for materials should be addressed to Fanny Kähnke.

Supplementary table 1: Health economic outcomes

Author Perspective (currency year)	Cost categories	Δ Costs	Health-related outcome	ICER[a]	CEA[b] P (WTP = 0); WTP (*p* = 0.5); WTP (*p* = 0.95)	QALY	ICUR[a]	CUA[b] P (WTP = 0; £20,000; £30,000)	CBA	Results[c]
Boiler, 2014 Societal (2009, €)	- Direct costs: medical, non-medical, intervention - Indirect costs: productivity losses Source: TiC-P	€1,471	Symptom severity (CES-D < 16, 5 score change)**[d]	€9,807 NE	22%; >€100,000	N.A.	N.A.	N.A.	N.A.	Unguided iPPI vs. WLC: ICER: £11,226 per symptom severity iPPI generated higher effects at higher costs.
Buntrock, 2017 Societal, Healthcare (2013, €)	- Direct costs: healthcare, patient costs (e.g., traveling, opportunity), medication, intervention - Indirect costs: productivity losses Source: TiC-P	Societal: €143 Healthcare: €136	Depression free years (DFY)**[e]	Societal: €1,117 NE Healthcare: €1,125 NE	Societal: 38%; €2,000[f] €9,680 Healthcare: 17%; €3,920[f]	EQ-5D-3L	Societal: €13,400 NE Healthcare: €13,500 NE	Societal: 38%[f], ≥60%[f] Healthcare: N.R., ≥ 64%	N.A.	Guided iCBT vs. TAU+: ICER: £1,170 (societal), £1,178 (healthcare)/depression-free year ICUR: £14,034 (societal), £14,139 (healthcare)/QALY gained iPST/BA resulted in greater effects and more QALY gained at higher costs.
Gerhards, 2010 Societal (2007, €)	- Direct costs: medical costs (healthcare sector), non-medical costs (travel, use of iCBT) intervention - Indirect costs: productivity losses Source: PRODISQ, patient reported healthcare use	iCBT vs. TAU: €-711 iCBT+TAU vs. TAU: €738 iCBT vs. iCBT+TAU: €-1,449	Symptom severity (BDI-II): reliable change index	N.R.	iCBT:70[f] TAU:13[f] iCBT + TAU+: 18[f], outperforms others with increased WTP (max. 80%)	EQ-5D	N.A.	iCBT:65%[f], 57%[f], 55%[f] TAU: 25%[f], 30%[f], 33%[f] iCBT & TAU: 10%[f], 12%[f], 14%[f]	N.A.	Unguided iCBT vs. unguided iCBT + TAU+ vs. TAU[Nb] Costs were lowest for the iCBT. There were no significant group differences in effect or QALY compared to iCBT plus TAU+ and TAU only. CUA and CEA tend to be in favor of iCBT.
Phillips, 2014 N.R. (N.R.., £)	- Direct costs: hospital, community, and healthcare services - Indirect costs: lost workdays (total absence) Source: CSSRI, self-assessed absence from work	£-35	N.A.	N.A.	N.A.	EQ-5D	N.R., SW	N.R.	N.A.	Unguided iCBT vs. AC: iCBT is less costly but generates lower QALYs.

Author	Cost categories	Δ Costs	Outcome	ICER	CEA	QALY	ICUR	CUA	CBA	Results
Titov, 2015 Healthcare, (N.R., AU$)	- Direct costs: healthcare resource use (admissions, consultations, medication use), intervention (therapist´s time) Source: resource use, health-care visits	$52	N.A.	N.A.	N.A.	EQ-5D-5L*[d]	AU$4,392 NE	8%[e], 95%[e], 95%[e]	N.A.	Guided iCBT vs. WLC: ICUR: £2,466/QALY gained iCBT resulted more QALY at higher costs.
Van Luenen, 2019 Societal, Healthcare (2017, €)	- Direct costs: intervention, healthcare - Indirect costs: productivity losses Source: TiC-P	Societal: €-731 Healthcare: €11	N.A.	N.A.	N.A.	SF-6D	Societal: N.R., SE Healthcare: N.R., NE	Societal: 95%[f],96%[f], 98%[f] Healthcare: 48%[f], 88%[f], 94%[f]	N.A.	Guided iCBT vs. AC + WLC: iCBT generated less (societal) and higher (healthcare) costs/QALY gained.
Brabyn, 2016 Healthcare (2012/13, £)	- Direct costs: service use, medication, intervention (only telephone support) Source: CSSRI	£591	N.A.	N.A.	N.A.	EQ-5D-5L	N.R., SE	50%, 55%, 55%	N.A.	Guided iCBT vs. unguided iCBT: Guided iCBT resulted in more QALYs gained at lower costs.
Geraedts 2015 Societal, Employer (2012, €)	- Direct costs: medical/non-medical costs, occupational health, intervention - Indirect costs: productivity losses Source: TiC-P, WHO-HPQ	Societal: €-714 Employer: €-508	CES-D, clinically significant change	Societal: €-6,645 SE Employer: €-4,664 SE	Societal: 62%, N.A., €44,000 Employer: 55%, N.A., €115,000	EQ-5D-3 L	Societal: €532,959 SW Employer: €382,354 SW	Societal: N.R.; max. 62% Employer: N.R.; max. 55%	NB: €508 BCR: €2.8	Guided iPST vs. TAU[Nb]: ICER: £-6,486 (societal), £-4,552 (employer)/significant change ICUR: £520,203 (societal), £373,203 (employer)/QALY gained iPST dominated regarding clinically significant change but resulted in less QALYs gained at lower costs.
Hollinghurst , 2010 Healthcare (inferred societal) (2007, £)	- Direct costs: NHS service use, personal expenditures, intervention (no costs for IMI/website) - Indirect costs: productivity (workdays lost) Source: resource use diary	£469	BDI "Recovery" (BDI <10)	£3,528 NE	N.R.	EQ-5D	£17,173 NE	0%[f]; 56%[f], 75%[f]	N.A.	Guided iCBT vs. WLC[Nb]: ICER: £4,686/recovered person ICUR: £22,810/ QALY gained iCBT resulted in greater effects and more QALY gained at higher costs.

Author	Cost categories	Δ Costs	Outcome	ICER	CEA	QALY	ICUR	CUA	CBA	Results
Klein, 2018 Societal, (2014, €)	- Direct costs: intervention, healthcare, participant - Indirect costs: productivity losses Source: TiC-P	€1008	Depression-free days	N.R., NE	40%, €50[f], max 65%	EQ-5D-3L	N.R., NE	18%, max 40%	N.A.	iPCT +TAU vs. TAU: iPCT resulted in greater effects and more QALY gained at higher cost.
Littlewood, 2015 Healthcare (2011/12, £)	- Direct costs: primary care, hospital, other community services, medication, intervention Source: GP medical records	iCBT1 vs. uGPC: £104 iCBT2 vs. uGPC: £-106	N.A.	N.A.	N.A.	EQ-5D	iCBT1 vs. TAU: £6,933 SW iCBT2 vs. TAU: dominated NW	iCBT1: 94%[f]; 42%[f] 38%[f] iCBT2: 0%[f], 0.04%[f]; 4%[f] uGPC: 6%[f]; 55%, 58%[f]	N.A.	Unguided iCBT 1 vs. uGPC [Nb]: ICUR: £7,838/QALY gained iCBT1 resulted in lower costs and less QALY gained. Unguided iCBT 2 vs. uGPC: iCBT2 resulted in higher costs and less QALY gained. uGPC alone compared with iCBT was most likely to be cost-effective.
Nobis, 2018 Societal (2013, €)	- Direct costs: healthcare services, medication, travel expenses, intervention - Indirect costs: domestic help, productivity losses Source: TiC-P	€97	Treatment response (CES-D): Reliable change Index and ≤ 23	€233 NE	48%; €250[f] €4,800[f]	EQ-5D-3L	€10,708 NE	46%; N.R., €14,000 = 51%	N.A.	Guided iCBT (1) vs. TAU+: ICER: £244/treatment response ICUR: £11,215/QALY gained iCBT resulted in greater effects and more QALY gained at higher cost
Romero-Sanchiz, 2017 Societal (2014, €)	- Direct costs: healthcare sector (GP, hospital stays), medication -Indirect costs: absenteeism Source: CSSRI	iCBT1 vs. TAU[+]: €-409 iCBT2 vs. TAU[+]: €41	BDI-II, point improve-ment*[g]	iCBT1 €-98 SE iCBT2 €10 NE	N.R.	EQ-5D-3 L*[g]	iCBT1: €-5,160 SE iCBT2: €497 NE	N.R.	N.A.	Unguided iCBT1 vs. TAU[+]: ICER: £-99/point improvement ICUR: £-5,201 per QALY iCBT1 dominated TAU[+] Guided iCBT2 vs. TAU[+]: ICER: £10/point improvement ICUR: £501/QALY gained iCBT2 resulted in greater effects and more QALY gained at higher cost.

Author	Cost categories	Δ Costs	Outcome	ICER	CEA	QALY	ICUR	CUA	CBA	Results
Warmerdam, 2010 Societal (2007, €)	- Direct costs: medical/non-medical costs (e.g., traveling, parking), intervention -Indirect costs: domestic help, productivity losses Source: TiC-P	iCBT vs. WLC: €256 iPST vs. WLC: €147 iCBT vs. iPST: €109	Clinically significant change (CES-D < 16)	iCBT vs. WLC: €1,817 NE iPST vs. WLC: €1,248 NE iCBT vs. iPST: €-36, NW	iCBT vs. WLC: 30%, €2,500[f], €25.000[f] iPST vs. WLC: 38%, €2,000[f], €35.000[f] iCBT vs. iPST N.R.	EQ-5D	iCBT vs. WLC: €22,609 NE iPST vs. WLC: €11,523 NE iCBT vs. iPST: N.R.	iCBT vs. WLC: 28%; 44%[f], 55%[f] iPST vs. WLC: 38%; 52%[f], 63%[f] iCBT vs. iPST: N.R.	N.A.	Guided iCBT vs. WLC: ICER: £2,147/clinical change ICUR: £26,713/QALY gained Guided iPST vs. WLC: ICER: £1,475/clinical change ICUR: £13,615/QALY gained iCBT vs. iPST: ICER: £43/clinical change iCBT and iPST resulted in greater effects and more QALY gained at higher costs compared to WLC.
Yan, 2020 Healthcare (2017, $)	-Direct costs: healthcare (physician, outpatient, inpatient services e.g., salaries, drugs, medical supplies) Source: Health administrative databases	SCP vs.SC: -$155 SCP vs. TAU: -$449 SCP vs. iCBT: -$161	N.A.	N.A.	N.A.	EQ-5D-5L	N.R.	SC: 26%[f], 27%[f], 28%[f] TAU: 18%[f], 11%[f], 7%[f] iCBT: 27%[f], 29%[f],30%[f] SCP: 29%[f], 33%[f], 34%[f]	N.A.	SCP vs. SC, TAU, unguided iCBT[Nb]: QALYs were highest in SCP, followed by SC, CBT, and TAU. SCP had a higher probability for cost-effectiveness than the three alternatives.
Bergström, 2010 N. R., (N.R., €)	-Direct cost: therapist´s and psychiatrist´s time Source: self-assessed therapist time	€-239	Responder ≥ 40% reduction on PDSS	N.R. SE	75%; N.R.	N.A.	N.A.	N.A.	N.A.	Guided iCBT vs. gCBT: iCBT dominates gCBT, generating more effect (responder) at less costs.
Dear, 2015 Healthcare (2013, AU$)	-Direct costs: primary, secondary care, therapist or supervisor costs, medication, internet access, computer, telephone use Source: patients' healthcare resource use	$92	N.A.	N.A.	N.A.	EQ-5D-5L*[h]	$8,806 NE	0%[f], 93%[f], 96%[f]	N.A.	Guided iCBT vs. WLC: ICUR: £4,825/QALY gained iCBT resulted in more QALYs at higher costs.

Author	Cost categories	Δ Costs	Outcome	ICER	CEA	QALY	ICUR	CUA	CBA	Results
Nordgren, 2014 N.R. (N.R., US$)	- Direct cost: healthcare, participant medication, intervention (therapists) - Indirect costs: productivity losses Source: TiC-P	CEA $-616 CUA $-474	CORE-OM defined as responder **[h]	$-1,824 SE	95%; N.A.	EQ-5D, N.R.	$-7,523, SE	90%, > 95%	N.A.	Guided iCBT vs. AC: ICERs: £-1,254/responder ICUR: £-5,173/QALY gained iCBT generated less costs and more effects and QALY gained.
Hedman, 2013 Societal, (2010, £),	-Direct costs: intervention (only therapists), healthcare, participant -Indirect costs: productivity losses Source: TiC-P	£-784	HAI, no diagnostic criteria for severe health anxiety**[i]	£-1,244 SE	64%; £4.800[f]	EQ-5D**[i]	£−6,533 SE	67%, 91%[f]	N.A.	Guided iCBT vs AC: ICER £-1,512/person without diagnosis on HAI ICUR; £-7,940/QALY gained iCBT generated less costs per effect and QALY gained.
Hedman, 2016 Societal, (2013, US$)	-Direct cost: intervention (only therapists), healthcare, participant costs - Indirect costs: productivity losses Source: TiC-P	$310	HAI, responder clinically significant improvement*[i]	$2,214 NE	9%; $2,300; $20,000[f]	EQ-5D, N.R.	$10,000 NE	N.R.	N.A.	Unguided iCBT vs. unguided iMA[Nb]: ICER: £1,633/responder ICUR £7,376/QALY gained iCBT resulted in higher effect and more QALYs gained at higher costs.
Hedman, 2011 Societal, (2009, US$)	-Direct costs: intervention (only therapists), healthcare, participant costs -Indirect costs: productivity losses Source: TiC-P	$-1335	LSAS < 43.3, responder	$-7,046 SE	81%; $70,000[f]	EQ-5D	$-17, 823 SE	81%, 82%[f],79%[f]	N.A.	Guided iCBT vs. gCBT: ICER: £-5,729/responder ICUR £-14,491/QALY gained iCBT generated more effect and QALY gained at less costs.
Hedman, 2014 Societal, (N.R., US$)	- Direct costs: intervention (only therapists), healthcare, participant costs - Indirect costs: productivity losses Source: TiC-P	$-808	LSAS < 43.3, responder	$10,100 SW	62%, max. 62%	EQ-5D	-$7,345 SE	Max. 62%, 39%[f], 34%[f]	N.A.	Guided iCBT vs. gCBT: ICER: £11,749/responder iCBT resulted in less effect at lower costs. ICUR: £-8,544/QALY gained iCBT generated less costs per QALY gained.

Author	Cost categories	Δ Costs	Outcome	ICER	CEA	QALY	ICUR	CUA	CBA	Results
Alaoui, 2017 Healthcare (2017, €)	- Direct costs: hospital space, IT usage, security, management, therapists Source: TDABC	€-343	N.A.	N.A.	N.A.	EQ-5D	N.R.	100%[f], 68%[f], 67%[f]	N.A.	Guided iCBT vs. gCBT: Both treatments were equally efficacious but iCBT generated less costs.
Powell, 2020 Societal, Healthcare, (2016/17, £)	- Direct costs: healthcare costs, intervention - Indirect costs: workdays lost Source: PSSRU, UK	Social: £-65 Healthcare: £-63	N.A.	N.A.	N.A.	SF-6D	Social: N.R SE Healthcare: N.R SE	N.R.	N.A.	Unguided iCBT vs. WLC: iCBT resulted in less costs per QALY gained.
Andersson, 2015a Societal Healthcare (2013, US$)	- Direct costs: therapist, healthcare, participant costs - Indirect costs: productivity losses Source: TiC-P	Societal $503 Healthcare $336	Y-BOCS, additional remission**[j]	Societal $931 NE Healthcare $672 NE	Societal 15%[f], $ 1100, $2600 = 90% Healthcare 0%[f], $700[f], $900[f]	EQ-5D-5L**[k]	Societal $7,186 NE Healthcare $4,800 NE	Societal 15%[f]; >95%[f] Healthcare 0%[f]; >90%[f]	N.A.	Guided iCBT vs. AC[Nb]: ICER: £687 (societal), £496 (healthcare)/remission ICUR: £5,301 (societal), £3,541 (healthcare)/QALY gained iCBT resulted in greater effects and more QALYs at higher costs.
Andersson, 2015b Societal, Healthcare (2013, US$)	- Direct costs: therapists, healthcare, participant - Indirect costs: productivity losses Source: TiC-P	Societal: $338 Healthcare: $242	Y-BOCS, relapse avoided	Societal: $1,489 NE Healthcare: $1,066 NE	Societal: 18%[f], $1500[f], $7000[e] Healthcare 0%, $900[f], $4250[f]	N.A.	N.A.	N.A.	N.A.	iCBT booster session vs. TAU[Nb]: ICER: £1,098 (societal), £786 (healthcare)/relapse avoided The additional booster session generated higher effects at higher costs.
Lenhard, 2016 Societal, Healthcare (2016, US$)	- Direct costs: healthcare use, supportive resources, drugs, intervention - Indirect costs: school absence, productivity losses Source: TiC-P	Societal: $-145 Healthcare: $21	Treatment responder >34% on CY-BOCS **[l]	Societal: N.R., SE Healthcare: $78 NE	Societal: 59.4%; N.R. Healthcare: 48%[f]; $200[f], $3000[f]	EQ-5D-Y	Societal: N.R. SW Healthcare: N.R.	N.R.	N.A.	Guided iCBT vs. WLC[Nb]: Societal: iCBT generated less costs per treatment responder. iCBT generated slightly less QALY at lower cost. Healthcare: ICER: £57/ treatment responder iCBT produced higher effects at higher costs.

Author	Cost categories	Δ Costs	Outcome	ICER	CEA	QALY	ICUR	CUA	CBA	Results
Lovell, 2017 Societal, Healthcare (2013/14, £)	- Direct costs: hospital and community-based health- and social-care services, medication, out-of-pocket expenses and savings, intervention - Indirect costs: productivity losses Source: AD-SUS, WHO´s HPQ	Healthcare iCBT vs. WLC: £138 SH vs. WLC: £364 iCBT vs. SH: £-226 Societal iCBT vs. WLC: £200 SH vs. WLC: £310 iCBT vs. SH: £-109	N.A.	N.A.	N.A.	EQ-5D-3L QALY	Healthcare iCBT vs. WLC: £32,857 NE SH vs. WLC: £55,152 NE iCBT vs. SH: £94,167 SW Societal iCBT vs.WLC: £48,095 NE SH vs. WLC: £46,970 NE iCBT vs. SH: £45,417 SW	Healthcare iCBT vs. WLC: 17%[f], 42%[e], 52%[f] SH vs. WLC: 0%[e], 0%[f], 8%[f] iCBT vs. SH: 95%[f], 88%[f], 85%[f] Societal iCBT vs. WLC: 15%[f], 28%[f], 35%[f] SH vs. WLC: 0%[f], 5%[f], 15%[f] iCBT vs. SH: 72%[f], 65%[f], 60%[f]	N.A.	Guided iCBT & Self-help vs. WLC[Nb]: Healthcare: ICUR: iCBT (£35,699), SH (£59,923)/QALY gained Societal: ICUR: iCBT (£52,255), SH (£51,033)/QALY gained iCBT and SH gained more QALY at higher costs. iCBT vs. Self-help: ICUR: £102,312 (healthcare), £49,346 (societal)/QALY gained iCBT had less costs and slightly less QALY gained.
Röhr, 2021 Healthcare (2019, €)	- Direct costs: healthcare costs, intervention, Source: CSSRI	€-100	N.A.	N.A.	N.A.	EQ-5D-5L	N.R.	81%; 38% 27%	N.A.	Unguided iCBT vs. TAU[+Nb]: iCBT generated lower costs per QALY gained.
De Bruin, 2016 Societal (2014, €)	- Direct costs: doctor visits, medication use, traveling expenses - Indirect costs: informal care, parents´ loss of (non) paid work, tutoring of adolescents Source: cost diaries (parents)	Societal: €-406 Healthcare: €147	Subjective sleep efficiency, Recovery (SE ≥ 85%)	€12,572 SW	95%, €12,000	EQ-5D	N.R. SE	95%, 70%[f], N.R.	N.A.	Guided iCBT vs. gCBT: ICER: £13,153 /recovered person iCBT produced less effect at less costs. iCBT generated slightly more QALY at less costs.

Author	Cost categories	Δ Costs	Outcome	ICER	CEA	QALY	ICUR	CUA	CBA	Results
Thiart, 2016 Buntrock, 2021	- Direct costs: healthcare intervention - Indirect costs: productivity losses	Employer: €-418	Positive treatment response (ISI)*[k]	Employer: €-1,512 SE	Employer: 87%, N.A., €761	SF-6D*[m]			NB: €417 BCR: €3.1	Guided iCBT vs. WLC: Employer: ICER: £-1,583/responder iCBT dominated WLC and produced a net benefit of £437 and a BCR of £3.2.
Employer, Societal, Healthcare (2013, €)	Source: TiC-P	Societal: €-991 Healthcare: €203	Symptom-free status (ISI)*[m]	Societal: N.R. SE Healthcare: €650	Societal: 94%, N.A., €1000 Healthcare: 6%, €500, €1500		Societal: N.R. SE Healthcare: €11,285	Societal: 94%, 98%, 99% Healthcare: 4%, 95%, 99%		Societal: iCBT dominated WLC generating more effect and QALY at less costs. Healthcare: ICER: £681/symptom-free status ICER: £11,819/QALY gained iCBT generated more effect and QALY at higher costs.
Ebert, 2018 Kählke, 2019 Employer Societal, (2013, €)	- Direct costs: health service uptake, patients' out-of-pocket costs, intervention costs - Indirect cost: productivity losses Source: TiC-P	Employer: €-189 Societal: €-380	Symptom-free status by Jacobson and Truax**[d]	Employer: €-521 SE Societal: €-1,063 SE	Employer: 67%, N.A., €1.500[f] Societal: 70%, N.A., €2.500[f]	SF-6D	Societal: N.R. SE	Societal: 71%[f], 76%[f],79%[f]	NB €181 BCR €1.6	Guided iMA vs. WLC: ICER: £-546 (employer), £-1,113 (societal)/symptom-free person iMA generated higher effects and QALY gained at lower costs, and a net benefit of £190 and a BCR of 1.06.
Lindsäter, 2019 Societal, Healthcare (2016, US$)	- Direct cost: healthcare, intervention -Indirect costs: productivity losses Source: TiC-P	Societal: $-77.24 Healthcare: $171.12	Remission rate on PSS (reliable change, post-rating PSS<31)**[d]	Societal: $-158 SE Healthcare: $349 NE	Societal: 60%, N.A., $1000 Healthcare: 12%[f], $400[f], $1000[f]	EQ-5D-3L	Societal: $-17,963 SE	Societal: 60%, 71%[f], 75%[f]	N.A.	Guided iCBT vs. WLC: Societal: ICER: £-115/responder ICUR: $-13,109/QALY gained iCBT generated more effect and QALY at less costs. Healthcare: ICER: £-255 iCBT generated higher effects and costs.

Author	Cost categories	Δ Costs	Outcome	ICER	CEA	QALY	ICUR	CUA	CBA	Results
Van Spijker, 2012 Societal (2009, €)	- Direct cost: health service uptake, patients' out-of-pocket costs, intervention, medication - Indirect cost: productivity losses Source: TiC-P	€-5039 (annualised costs)	Treatment response (improvement of 6.48 on BSS)*[n]	€-34,727 SE	91.5%, N.A., €18,000[f]	N.A.	N.A.	N.A.	N.A.	Unguided iCBT vs. WLC+: ICER: £-39,753/responder iCBT generated less costs per responder.

Note:
AC Attention control group, *AD-SUS* Adult Service Use Schedule, *BDI* Beck's Depression Inventory, *BSS* Beck Scale for Suicide Ideation, *CBA* Cost-benefit analysis, *CG* control group, *CEA* Cost-effectiveness analyses, *CEAC* cost-effectiveness acceptability curve, *CES-D* Center of Epidemiologic Studies Depression Scale, *CORE-OM* Clinical Outcomes in Routine Evaluation–Outcome Measure; *CUA*, Cost-utility analyses; *CSSRI*, Client Sociodemographic and Service Receipt Inventory, *CY-BOCS* Children's Yale-brown obsessive compulsive scale, *Δ Costs* Mean incremental costs per participant (intervention group minus control group), *EQ-5D-3L/5L* European quality of life index version 5D with 3 or 5 level, *F2F* Face-to-face, *FU* Follow-up, *gCBT* Group-administered cognitive-behavioural therapy, *HAI* Health Anxiety Inventory, *iCBT* internet-based cognitive behavioural therapy, *ICD* International Classification of Diseases, *ICER* incremental cost-effectiveness ratio, *ICUR* incremental cost-utility ratio, *IG* intervention group, *iMA* internet-based interventions applying mixed approaches, *iPPI* internet-based Positive Psychology Intervention, *iPST* internet-based problem-solving therapy, *iPCT* internet-based preventive cognitive therapy, *ISI* Insomnia Severity Index, *LSAS* Liebowitz Social Anxiety Scale, *Max.* maximal probability of cost-effectiveness, *N.A.* not applicable, *N.R.* not reported; *p* probability of a treatment being cost-effective when compared with a control condition**,** *PDS-5* Posttraumatic Diagnostic Scale for DSM-5, *PSSRU* Personal Social Services Research Unit, *PDSS* Panic Disorder Severity Scale, *PHQ-9* Patient Health Questionnaire-9, *PRODISQ* PROductivity and DISease Questionnaire, *PSS-10* Perceived Stress Scale, *SC* Standard Care, *SCP* Stepped care pathway, *SE* Subjective sleep efficiency, *SF-6D* Short From six dimensions based on SF-36 Health Survey, *SPIN-17* Social Phobia Inventory, *TAU* Treatment as usual, *TAU*+ Treatment as usual with additional information e.g. web-based psychoeducation, *TDABC* Time-driven activity-based costing method, *TiC-P* Trimbos/iMTA Questionnaire on Costs Associated with Psychiatric Illness, *uGPC* Usual General Practitioner Care, *Vs.* versus, *WHO HPQ* World Health Organization Health and Work Performance Questionnaire, *WLC* Wait list control condition, *WLC+* WLC with additional information during the waiting period, *Y-BOCS* Yale-Brown Obsessive-Compulsive Scale, *AU$* Australian Dollar, *€* Euro, *£* Pound Sterling, *US$* USDollar

The significance level *$p<0.05$, ** $p<0.001$ for health-related outcomes and QALY are stated, if reported
Cost-benefit analysis was interpreted using this formula: CBA = NB>0, BCR>1, and ROI>0% = financial returns

[a] According to the location of the point estimate in the incremental cost-effectiveness plane the abbreviation South-East (SE), North-East (NE), South-West (SW), and North-West (NW), was used to indicate +/- cost and effects of the intervention compared to the control condition: SE ICERs are located in the south-east quadrant meaning that the intervention is more effective at lower costs (dominant); NE ICERs are located in the north-east quadrant meaning that the intervention is more effective at higher cost; NW ICERs are located in the north-west quadrant meaning that the intervention is less effective at higher cost (dominated); SW ICERs are located in the south-west quadrant meaning that the intervention is less effective at lower cost
[b] The WTP given certain probabilities of CE (e.g., probability of CE if the WTP is zero, *P* (WTP = 0) based on the CEAC are reported. The probabilities of the CE given certain WTP thresholds (e.g., for a WTP of £20,000, there is a 95% intervention's probability of being cost-effective, WTP ($p = 0.95$) based on the CEAC are reported.
[c] All outcomes were indexed to a 2020 reference year and converted to Pound Sterling (£) using purchasing power parities (PPPs)
[d] The χ^2 test was used for statistical analysis
[e] The independent *t*-test was used for statistical analysis
[f] The probability of the ICER given a specific WTP threshold or the WTP according to a given probability was not stated, thus the value was estimated based on the CEAC

[g] One-way ANOVAs (analysis of covariance) were used for statistical analysis
[h] A linear mixed model with restricted maximum-likelihood estimation (REML) and an unstructured (UN) covariance structure was used for statistical analysis
[i] Mixed-effects model analyses were used for statistical analysis
[j] A logistic regression model was used for statistical analysis
[k] A linear regression model was used for statistical analysis
[l] The Fisher's exact test was used for statistical analysis
[m] A bootstrapped seemingly unrelated regression equation model (bias-corrected accelerated 95% Cis) was used for statistical analysis
[n] A linear probability model considering the clustered data structure was used for statistical analysis
[Nb] The net-benefit approach was used for the analysis (net-benefit regression framework)

Supplementary table 2: Medical subject headings (MeSH) used for searching the Medline data base.

Building blocks	Treatment	Disorder	Delivery mode	Costs	Randomized trial
MEDLINE	"Psychotherapy"[mh] OR Psychotherap* OR Therap* OR Intervention OR Treatment OR Prevent* OR prevention	"Depression"[mh] OR depress* OR mood OR Bipolar OR Dysthymi* OR mania* OR anxi* OR Stress* OR Phobi* OR Panic* OR agoraphobi* OR social anxi* OR generali* anxi* OR GAD OR OCD OR "Obsessive–compulsive disorder"[mh] OR PTSD OR post-traumatic stress OR health anxiety OR hypochondria OR self-harm OR suici* OR sleep* OR insomnia	"Computer Assisted Therapy"[mh] OR Internet[mh] OR "Computer-Assisted Instruction"[mh] OR Online OR Online based OR Web OR Web based OR Internet OR Internet based OR World wide web OR Computerized OR computer	"Costs and Cost Analysis"[mh] OR "Cost-Benefit Analysis"[mh] OR "Healthcare Costs"[mh] OR "Cost of Illness"[mh] OR "Quality-Adjusted Life Years"[mh] OR Economic OR Cost utility OR Health economic OR Cost*	Efficacy OR "Randomized Controlled Trials as Topic"[mh] OR "Randomized Controlled Trial"[mh] OR Randomized controlled trial OR Randomized trial OR RCT

4. General Discussion

4.1 Aims of this thesis

The primary aim of this thesis is to support decision-makers' informed choice when allocating scarce resources in the health sector. This discussion section summarizes and examines the findings of three studies by answering the following questions:

How do the studies' results compare to previous research on internet- and mobile-based interventions (IMIs) targeting social anxiety disorder (SAD) and stress, and to existing systematic evidence on health economic effects? What are the limitations of the presented studies? What are the clinical implications? What future research is still needed? Finally, a brief general conclusion of this thesis is presented.

4.2 Main findings

Below, a summary of the main findings of this thesis is presented. For an extended version, see the included studies' overall summary or the specific articles respectively. In Study One, results from our randomized controlled trial (RCT) of an unguided web-based intervention targeting SAD in students indicated moderate and large effect sizes on SAD symptoms for the intervention as compared with the waitlist control (WLC) group at post-treatment. Effects were sustained at 6-month follow-up (FU). In addition, the intervention showed a promising likelihood of being more cost-effective from both a societal and healthcare perspective compared with the WLC group with access to usual care.

In Study Two, the health economic evaluation of a guided internet-based stress management intervention (iSMI) was compared with WLC. The intervention yielded a positive net benefit, revealing a favorable likelihood of being cost-effective per additional symptom-free person when examined from the employer's perspective. From the societal perspective, the iSMI showed a promising likelihood of being cost-effective compared with the control group, achieving an additional symptom-free person and a quality-adjusted life year (QALY) gained.

In Study Three, a systematic review on cost-effectiveness of IMIs for the prevention and treatment of common mental health problems found that guided interventions targeting depression and anxiety had favorable probabilities of being more cost-effective when compared

with various control conditions. Though, more evidence was needed to draw further conclusions.

4.3 Comparison with previous research

4.3.1 Study 1

This RCT of an unguided self-help intervention targeting students diagnosed with SAD is one of few in existence. Treating SAD in students yielded moderate to large between-group effect sizes on the primary outcome measures at post-treatment (Social Interaction Anxiety Scale (SIAS): *d* = 0.55, 95% confidence interval (CI) [0.27, 0.83]; Social Phobia Scale (SPS): *d* = 0.76, 95% CI [0.47, 1.04])[95] that were maintained at 6-month FU (SIAS: *d* = 0.59; 95% CI [0.30, 0.87]; SPS *d* = 0.83, 95% CI [0.54, 1.1])[144].

These findings are in line with the results of a recent systematic review and meta-analysis on internet-based cognitive behavioral therapy (iCBT) for SAD[145]. The effect sizes were moderate to large for both unguided iCBT (*g* = 0.68, 95% CI [0.94, 0.41]) and guided iCBT (*g* = 0.81 95% CI [0.63, 0.99]) compared with WLC at post-treatment[145]. Subgroup analysis yielded no significant difference in effects of iCBT compared with face-to-face (F2F) cognitive behavioral therapy (CBT) (*g* = -0.07; 95% CI [-0.24, 0.10]) or guided internet-based CBT (iCBT) compared with unguided iCBT (χ^2 = 0.96, df = 2, *p* = 0.62, I2 = 0%)[145]. Effects on SAD could be maintained after 6 months (*g* = -0.08, 95% CI [-0.27, -0.11]) and at 12 months (*g* = -0.17, 95% CI [-0.34, -0.01]).

To date, two other studies not included in the meta-analysis have examined the effects of CBT in unguided IMI targeting SAD patients in the general population. The first study compared transdiagnostic CBT to disorder-specific CBT and guided versus self-guided internet-delivered treatment, yielding only minor differences between groups[146]. The self-guided intervention resulted in large within-group effect sizes (*d* = 1.01, 95% CI [0.71, 1.30]) from pre to post-treatment and from pre to 12 months follow-up (*d* = 1.5, 95% CI [1.19, 1.82])[146]. The results are comparable to the effect of our study at post-test (for instance, SPS *d* = 1.14 (95% CI [0.71, 1.30]) and at 6 months (SPS, *d* = 1.27, 95% CI [0.96, 1.57]). The second study (N = 2,116) found a significant change in the Social Phobia Inventory (SPIN-17) score of -1.94 (95% CI [-3.13, -0.75]) between intervention and WLC group, equating to small and persistent effects at post-test (*d* = 0.2, pooled standard deviation (SD) 9.81) that were maintained at 12 months (-3.07, 95% CI [-4.32, -1.82])[147]. This small effect might be explained by the large number of participants reporting subclinical symptoms and not meeting diagnostic criteria for SAD (SPIN-17:

Mean 39.61 [SD 13.14]). Also, in contrast to our study, the trial was fully automated, including no researcher contact to promote engagement or adherence to the intervention.

In addition, our intervention showed small to large between-group effects sizes on the secondary outcomes having *d* = 0.23 (95% CI [0.05, 0.50]) on QALYs, *d* = 0.45 (95% CI [0.17, 0.73]) on depressive symptoms, and *d* = 0.76 (95% CI [0.47, 1.05]) for social anxiety symptoms (measured via Liebowitz Social Anxiety Scale (LSAS)) at 6-months FU. These effects were lower compared to the first study[146] and higher compared to the second study[147], possibly due to symptom severity at baseline moderating the intervention effect[148].

On the topic of university students, two other studies examined fear of public speaking[69,76] and SAD. These were already included in the previous meta-analytic evidence[144]. One additional IMI focusing on a non-clinical sample of university students with SAD symptoms yielded a small effect (t_{172} = 2.21, *p* = 0.04, *d* = 0.32) compared with WLC at 4 months post-test[149]. Again, these smaller effects (compared to our study) may be explained by the usage of a non-clinical sample. Non-clinical samples are characterized by lower baseline scores and severity of SAD symptoms, resulting in less potential room for growth or improvement, which could limit the observed treatment effect.

To the best of my knowledge, this was the first trial-based health economic evaluation of an unguided self-help intervention in university students diagnosed with SAD. The intervention generated lower costs (€-321, 95% CI [-862, 66]) and significant QALY gains (0.046, 95% CI [0.024, 0.68]) compared with the control group. Thus, the IMI was the dominant treatment option, showing a 92%–93% probability of being cost-effective when compared to WLC (from a societal perspective) at a willingness to pay (WTP) of €0 per symptom-free status and QALY gained. From the healthcare perspective, higher effects at higher cost were generated, leading to a 96% likelihood of the intervention of being cost-effective compared with WLC at a WTP of €6,000 per symptom-free status and QALY gained.

There currently exist only three other economic evaluation of IMIs targeting SAD. One guided IMI generated less costs and better effects and showed acceptable probabilities of being cost-effective at 6-month (81%)[88] and 4-year FU (61%)[150] at WTP of zero, compared with group CBT. Another study compared a guided IMI to a F2F treatment and examined the costs for the therapist time only[90], which resulted in unclear findings due to lack of reporting. The third study and sole other economic evaluation of an unguided IMI compared with a WLC was judged to be cost-effective. A cost utility analysis from a healthcare and social care perspective at 12-month FU showed that the IMI was cost-effective and dominant, with less costs and more QALYs gained compared with WLC. Unfortunately, the probability of cost-effectiveness was not

reported, thus no further comparison can be made[147]. Despite methodological differences, evidence is converging to support favorable levels of cost-effectiveness and cost-savings.

4.3.2 Study 2

Two health economic analyses of this iSMI targeting employees with elevated stress were conducted from an employer's and the societal perspective. The between-group effect size of the iSMI on perceived stress (d = 0.83[151]) was in line with meta-analytic evidence of SMI and systematic evidence of workplace interventions[81,152–154]. To the best of my knowledge, no evidence exists regarding the cost-effectiveness of an iSMI compared with WLC. However, there exists cost-effectiveness evidence of interventions targeting mental health symptoms at the workplace and two internet-based interventions demonstrating positive effects and cost reductions from the employer's perspective.

A recent systematic review on cost-effectiveness found that interventions targeting employees with elevated risk for mental health problems were cost-saving, reporting a return of investment (ROI) of US$1.5 to US$7 per 1 dollar invested respectively[155]. Our study showed comparable results generating €1.61 per 1 euro invested in the intervention (61% of profit per euro invested; 95% CI [-220, 350]). Additionally, our study yielded a positive net benefit of €181 (95% CI [-643, 1042]). This supports the existing health economic evidence of two IMIs at the workplace analyzed from the employer's perspective. One study on insomnia showed a positive net-benefit of €418 (95% CI [593.03, 1488.70]) per participant and a ROI of 208% (95% CI [-296.52, 744.35])[156].

Another intervention targeting workers with depressive symptoms compared with care as usual showed a ROI of 178% (95% CI [-2466, 2863]) and a net benefit of €508 (95% CI [-7029, 8160])[157]. The intervention's probability of being cost-effective in comparison to control group per clinically significant change was 55% at a WTP of 0 compared with 67% in our study. Yet, this study only resulted in very small and non-significant clinical changes between groups.

Our economic evaluation from the societal perspective showed an acceptable likelihood that the intervention is cost-effective compared with WLC. When the society is not willing to pay anything to get an additional positive outcome (WTP = €0), there was a 70% and 69% probability that the intervention is more cost-effective than WLC per symptom-free person and QALY gained, respectively. At a conservative WTP threshold of €20,000 (US$25,800) per QALY gained this probability rose to 76%. Our results match findings of a study on stress-related

adjustment and exhaustion disorder showing that guided iCBT dominated WLC regarding remission rate and QALYs gained, respectively, showing an 60% probability of cost-effectiveness at a WTP of £0 for both outcomes from a societal perspective after 3 months[158]. Likewise, a study comparing an iSMI to an iCBT for adults with severe health anxiety showed large effect sizes and cost reductions for both interventions. Yet, the iCBT was judged cost-effective compared with iSMI, which generated higher costs per clinical significant improvement and QALY gained[159].

4.3.3 Study 3

The rationale for conducting the systematic review on cost-effectiveness of psychological IMIs targeting mental symptoms was founded in the desire to generate more evidence of IMI's cost-effectiveness compared to other treatment options. This was necessary due to outdated systematic evidence and few available health economic evaluations. Over the past five years, many more studies were conducted, which has prompted several new reviews of cost-effectiveness related to specific fields, disorders, or age groups. Yet, the overall number of studies is still limited, and while some evidence is promising, other evidence is inconclusive.

To date, only two systematic reviews focused on a wider range of mental health problems in IMIs. The first review only included studies published until the year 2014[85]. The second, more recent review on major depressive and anxiety disorders, focused on a variety of different intervention types (screening, diagnostic, observational) that often only reported costs, but contained no full health economic evaluations[160]. Both systematic reviews and our findings indicated that guided IMIs targeting anxiety and depression show a favorable likelihood of being more cost-effective in comparison to control groups. The results are consistent with previous reviews of these disorders[86,87,161]. Furthermore, reviews on a wider range of interventions in mental health prevention and promotion[155] and depression prevention[161] showed the potential to be cost-effective and cost-saving, but highlight that more evidence is needed before firm conclusions may be drawn. In our review and others, the findings and conclusions are limited by inconsistent evidence, to the high heterogeneity of included studies, and non-adherence to economic reporting standards. In general, evidence gaps have been identified in under-researched disorders[162,163], in low and middle income countries[164], and in youth[165].

The health economic evaluations I conducted focus on the prevention (Study Two) and treatment (Study One) of mental disorders and are only a few of the many new studies showing acceptable to high probabilities of IMIs being cost-effective. Based on the accelerated growth

of health economic studies in the recent years, we can soon expect the newly bolstered body of evidence to facilitate drawing further conclusions about the cost-effectiveness of IMIs in mental health.

4.4 Limitations

Study One showed promising results and relatively low attrition rate at 6-month FU compared with other unguided studies[166]. It had balanced participant characteristics, included a full health economic evaluation that adhered to guidelines and yielded robust findings across sensitivity analyses. Study Two likewise yielded favorable results based on two full health economic evaluations. Nevertheless, several study limitations such as design imperfections, the used comparators, the reliance on self-reported data, and the limited time-horizon need to be considered and are discussed for both studies below as they share common characteristics.

First, a WLC group design with unrestricted access to treatment as usual (TAU) was used. Before starting the trial, patients were informed about how and where to seek help if needed, and the patients' use of medication or TAU (e.g., psychotherapy) remained unrestricted. Nonetheless, potential nocebo effects (e.g., worsening of symptoms) could have appeared in the control condition[167]. Patients in the WLC experienced delayed access to the treatment and may have been less motivated to seek additional help, resulting in overaccentuated treatment effects[168]. As recommended for health economic evaluations[169], a standard care comparator (e.g., F2F treatment) would have been superior for informing decision-makers on different potential treatment options.

Second, the time horizon of the studies was limited to 6 months beyond which no conclusions about effects and costs can made. Longer FU periods are required to fully assess the sustainability of effects, i.e., to measure the effects and costs of lagging or intangible costs. A longer FU period could likewise observe the effects of SAD on students' performance leading to prolonged academic studies, university drop-out and/or poorer qualifications. At the workplace, a longer study period might have been able to measure costs of staff turnover and premature retirement.

Third, most outcomes were assessed using self-reported instruments (apart from SAD symptoms, which were assessed via diagnostic interviews). Common limitations to this approach are the "social desirability bias[170]" and "recall bias[171]" that may affect the results. As an example, although self-reporting absenteeism and presenteeism is a standard procedure for RCTs[172] with good reliability and validity[173], it may lead to over- or underestimating costs.

Notwithstanding, possible bias did not vary systematically between groups due to the groups having balanced characteristic.

Fourth, the generalizability of our findings is restricted to similar settings. Our results apply to students from German speaking countries. Different student characteristics such as language or different beliefs in or views of mental health may lead to other results. In Study Two, the self-selection of participants led to a predominance of the female sex (73%) and higher education (77%) compared to the general population. Evidence suggests that these characteristics increase adherence[174] or minimize drop-out[175], as participants have an increased motivation to participate in the intervention and are therefore more responsive. The effects of the intervention may differ compared with populations with lower education or a higher proportion of male participants. Additionally, costs of productivity were estimated using the participants' wages, which were higher than the average wage.

Fifth, both trials were powered to detect effects on the primary clinical outcome, which is common in health economic evaluations conducted alongside a clinical trial. However, economic analyses require greater sample sizes due to a higher variance in costs[176]. For this reason, a probabilistic decision-making approach, that informs the decision makers on probabilities rather than on statistical significance, was used to address this issue[177]. If more evidence had been gathered, a meta-analysis based on pooling individual patient data could have better addressed the insufficient power[178].

Sixth, the randomized-controlled nature of these studies is characterized by high research attention in the form of strict inclusion procedures (requiring informed consent, self-report assessments, diagnostic interviews). These procedures are thought to lead to an overestimation of treatment effects based on research attention and self-selection[179]. Screening and interviews may cause the self-selection of mainly highly motivated individuals that cannot always be expected in routine care. Hence, the findings might not be generalizable to unguided self-help interventions that do not benefit from these research procedures. Also, RCT procedures can function as an adherence-promoting factor, strengthening a participant's commitment to partake in the intervention. This might be of particular importance for self-help interventions that are implemented under routine conditions. Here alternative adherence promotion elements are advised[63].

Last, research participation can modify effect outcomes through the Hawthorne effect. This effect is described as the change in participants' behaviors by virtue of being observed[180].

Only a few conclusions could be drawn from Study Three despite concerted efforts to improve the comparability of the included studies' results by converting currencies,

establishing criteria and thresholds for the cost-effectiveness, and only including full health economic evaluations.

First, the heterogeneity of studies was very high, hampering the comparability of the evidence. Study designs, methods used, outcome measures, comparators used, and economic perspectives taken varied widely between studies. As an example, I argued before that the use of different comparators alone already influences the outcome as well as the costs. The same is true for the calculation of intervention costs that mostly do not include development or adaptation costs of an intervention.

Second, the interpretability of cost-effectiveness estimates was restricted due to missing WTP thresholds for disease specific measures. For example, the monetary value of a depression-free person gained to society or the healthcare system is unknown. Here, but also for common thresholds, other aspects are relevant for decision-makers to reach informed decisions such as the burden of disease, acceptability, the prognosis of a disease, or medical ethical questions.

Third, limitations that can be found in many health economic evaluations alongside RCTs are also reflected in this review: the need for longer time intervals, underpowered studies leading to non-significant differences in QALYs or costs between groups, missing uncertainty analysis in form of a cost-effectiveness (CE) plane, or non-adherence to reporting standards.

Last, the generalizability of the results is limited to the Western countries, mostly countries in North-West Europe. Future studies need to be conducted in other countries and regions to learn more about the impact of cultural differences (e.g., employee's morale)) on effects and costs of psychological internet-based interventions.

4.5 Clinical Implications

4.5.1 Study 1

While SAD is one of the most frequent mental disorders, many affected individuals remain untreated. This leads to isolation that negatively affects education and occupation. SAD generates high indirect costs due to presenteeism and absenteeism compared with relatively low direct costs. Excess costs of SAD in Germany were estimated at 451 Euro over a timeframe of 6 months including both direct costs (e.g., in- and outpatient treatment) and indirect cost due to absenteeism from work[181].

Findings of our study strengthen the evidence base suggesting that unguided IMIs are an effective, low-threshold and cost-effective way to reduce SAD symptoms and other related

adverse effects. The German SAD S3 treatment guideline[182] acknowledges IMIs based on CBT only as an add-on to F2F treatment or while waiting for F2F psychotherapy. However, given the positive results of the presented studies and several recent developments, I strongly suggest establishing unguided IMIs for SAD as a viable treatment option in student mental healthcare that can help address certain barriers to service seeking or service provision.

First, one third of students in our study self-reported as unwilling to use any F2F treatment[183]. This can be explained by the nature of SAD as individuals with this disorder tend to avoid F2F contact so as not to be evaluated negatively or stigmatized. In addition, students commonly attempt solving their mental problems on their own[184], which—in combination with a general lack of skilled psychotherapists—leads to a delayed treatment provision. Thus, IMIs offer a low-threshold treatment to reach those students compared to F2F treatment.

Second, recent systematic and meta-analytic evidence indicates that iCBT creates equivalent effects when compared with F2F treatment in anxiety disorders[185]. iCBT is recommended as a first-line treatment without the addition of auxiliary treatment measures[145].

Third, the COVID-19 pandemic further increased the unmet need of help by exacerbating the overloaded mental healthcare management both within and outside of the university setting and decreasing social contacts leading to isolation[186]. Left untreated, these students could manifest SAD symptoms, potentially leading to a lower quality of life, isolation, academic failure, study drop-out, and diminished job prospects. This not only negatively impact individuals' well-being but also generate enormous costs in the long run. Thus, IMIs as treatment option are essential to address this unmet need.

Fourth, scaling up digital intervention leads to increased provisioning and uptake. The resulting low marginal costs make digital interventions a viable tool to generate effects at population level or within a university setting. Such a scale-up is further facilitated in unguided interventions due to the absence of human guidance[187].

The results of the study are limited to a clinical sample. More than 800 students showed interest in our study. However, only 200 were included, usually because they failed to meet the clinical cut-off, dropped out to avoid interviews, or because the diagnostic interviews did not confirm the diagnostic status. The inclusion of students with subclinical SAD symptoms could easily extend the IMI's reach. This would also better reflect the population that seeks help at a university mental healthcare service. Additionally, the intervention might help to decrease the risk of students with subclinical SAD symptoms of developing a full-blown disorder. Nonetheless, an increased reach may diminish the intervention's effect, due to, e.g., symptom severity moderating treatment effects[147] or because the absence of diagnostic interviews reducing

adherence. This can be explained through the concept of symptom severity moderating treatment effects and because the absence of diagnostic interviews reduces adherence[148]. In general, lower adherence can be observed in unguided interventions, subclinical patients or under routine care conditions due to reduced structuring and absent research attention compared to a RCT[188]. Under these circumstances adherence-promoting elements need to be applied to secure treatment adherence.

The study's intervention is based on the well-established cognitive behavioral approach proposed by Clark and Wells[96]. An additional treatment module on fear of positive evaluation (FPE), a neglected target of SAD treatment, is offered. Weeks and Howell's[189] bivalent fear evaluation model presents the fear of negative and positive evaluation as important treatment elements[104]. FPE can prevent patients from making progress, as they feel discomfort instead of pride when receiving positive social feedback. Originally, the study was designed to compare two active conditions with and without a module on FPE to quantify its potential treatment effect. However, changes in the study design in favor of the health economic evaluation impeded this approach. The results showed moderate significant effects of the IMI compared with WLC on the Fear of Positive Evaluation Scale (d = 0.54, 95% CI [0.26, 0.82]) and Disqualification of Positive Social Outcomes Scale (d = 0.56, 95% CI [0.82, 0.55]). Yet, higher within-group effects on SAD were observed when compared with another study based on the same self-help IMI that did not include the module on FPE[190]. Thus, the benefits of a FPE treatment module remain unclear.

4.5.2 Study 2

Stress comes in many forms and is commonly labeled as chronic, perceived, traumatic or work-related stress. Based on data collected by the largest German statutory health insurance (SHI) ("Techniker Krankenkasse"), perceived stress has increased over the past decade, resulting in one out of four persons feeling stressed frequently (26%)[191]. The main stressors were of a work-related nature and high expectations of oneself. The impact of alleviating work stress alone is estimated as annual cost savings of €1,753 to €3,010 for absenteeism and of €188 to €582 for presenteeism per employee according to a German pharmaceutical company[192]. Yet, the reach of F2F interventions is limited by financial, spatial, and time barriers. iSMIs can overcome these barriers, are easily scaled-up, and can minimize resources (especially when proven cost-effective) leading to increased treatment uptake. If implemented successfully and used widely, preventive iSMIs show the potential to reduce the adverse effects of

persistent stress at the workplace and the general disease burden of mental disorders as well as costs of related productivity losses at the population level[193]. Findings of a recent meta-analysis support the iSMI's potential to reduce symptoms of depression and anxiety symptoms. iCBTs targeting elevated stress were found to be effective, showing large effects on anxiety (*d* = 0.69 95% CI [0.52, 0.86] and depression (*d* = 0.65, 95% CI [0.56, 0.75])[154].

Further evaluations of Study Two's iSMI shed more light on the iSMI's preventive effect. A three-armed trial, compared the iSMI with either adherence-focused guidance (AFG) or no guidance (self-help, SH) to a WLC group[194]. Both intervention groups had moderate to high effects on stress (SH, *d* = 0.91; AFG, *d* = 0.85) and depression (SH, *d* = 0.62, AFG, *d* = 0.74). The results revealed that the iSMI's effect on depressive symptomatology was mediated by perceived stress and resilience. Thus, the authors suggested that preventive iSMIs should be designed for both stress reduction and enhancing health promoting factors (e.g., resilience). These findings match the results of another study, which offered the same iSMI to university students with elevated levels of depression (CES ≥ 16) compared with an internet-based psychoeducational program. This study's findings showed small effects on depressive symptom severity (*d* = 0.36)and anxiety (*d* = 0.35)[195].

Study Two's findings suggest that the iSMI is cost-effective in highly stressed employees. Yet, treatment effects on moderately stressed employees remained unclear. A universal prevention study, applying no baseline inclusion criteria, showed that this iSMI yielded large effects on perceived stress at 6-month FU (*d* = 0.61)[196]. Moreover, resilience, agreeableness, psychological strain, and self-regulation were identified as having a moderating effect on the intervention's main effect. Thus, initial evidence suggests a broad applicability of this iSMI and consistent effects under routine care conditions.

Even though adherence is assumed to be higher for guided iSMI[188], no other health economic evaluation has assessed the economic impact of different guidance formats. However, a large share of intervention costs is based on human support offered during treatment, and the difference in effects between the guided and unguided iSMI was only small. In two studies, the iSMI was found to be effective when offered either with AFG (*d* = 0.85)[197] or SH (*d* = 0.65)[198] compared to WLC. In another study, similarly large within-group effects and no significant between-group effects were found when comparing the SH iSMI to the AFG iSMI.[194] Therefore, SH iSMIs show similar effects and lower intervention costs compared to guided iSMI, and thus might be cost-effective.

In practice, evidence based on health economic evaluations is not required for digital interventions to be considered for reimbursement by the German healthcare system. Hence,

health economic evaluations have no impact on decision-making, possibly not warranting further research on this iSMI. The Digital Health Care Act (2019) entitled every person insured under the German SHI to the provision and reimbursement of digital health applications (DiGA). In a simplified process, DiGA can become eligible for reimbursement if they fulfill general requirements (i.e., safety, data protection) and show positive effects (i.e., medical benefits)[199]. Consequently, in October 2021, the iSMI evaluated in Study Two was approved as DiGA ("HelloBetter Stress and Burnout")[200]. As a listed DiGA, the iSMI is officially available to reduce difficulties in coping with life and work stress for adults aged 18 to 65 years.

The last perspective on clinical implications of Study Two is based on the German Guidelines in Prevention[201] published by the National Association of Statutory Health Insurance Funds ("GKV-Spitzenverband", GKV-SV) based on the Social Code Book V §20. Referring to this, health promotion in occupational healthcare consists of several areas of action and principles of prevention relating to external working conditions (e.g., workplace design, leadership, a physical activity facilitating environment) and internal individual work and lifestyle factors (e.g., stress management, resilience, healthy nutrition). In prevention and health promotion, an iSMI represents an effective behavioral intervention. However, only by combining interventions targeting the individual's behavior and interventions creating positive working environments can we create sustainable and healthy working conditions.

4.5.3 Study 3

The results of Study Three may have several important implications for decision-makers allocating scarce resources. Mental disorders pose a great burden on society and the economy, necessitating a sustainable healthcare approach for the many in need of it. Due to the excessive demand of (mental) healthcare services, limited personnel resources, and strict contact restrictions caused by the COVID-19 pandemic, healthcare service providers moved away from F2F treatment and scaled up effective digital mental healthcare options. As a result, the benefit of internet-based psychological (preventive) interventions (including cost-effectiveness benefits) has increased in relevance.

The implications of our findings are relevant to countries using health economic evidence in their decision-making process, in contrast to the decision-making practice in Germany. Recommendations for policy makers and relevant stakeholders include:

(1) low intensity psychosocial interventions, such as guided IMIs targeting depression and anxiety, are viable treatment options;

(2) evidence for under-researched disorders and unguided IMI is limited, yet the use of low-threshold, self-help IMIs is warranted on a case-by-case basis given their scalability and potential effects on population level; and

(3) to secure the treatment effects in routine care, among others, implementation setting, target population, and stakeholder views need to be considered to optimize the allocation of scarce resources (i.e., for priority setting).

In addition to the above recommendations, it is also important to consider the different governmental reimbursement mechanisms of IMIs (e.g., United Kingdom: National Institute for Health and Clinical Excellence [NICE], Germany: DiGA). Other criteria than effects and costs that may likewise be important are: interoperability, patient safety, and data security[199].

4.6 Challenges and directions for future research

Studies One and Two strengthen the existing evidence for the efficacy of internet-based psychological interventions for improving mental and work-related outcomes. Despite, their large role for the evidence for cost-effectiveness of IMIs (due to the limited number of current studies available), more studies on SAD and elevated stress are required to confirm their results. The presented systematic review (Study Three) confirmed the limited number of health economic evaluations alongside IMIs.

In the following section, several existing and future challenges for IMIs are discussed derived from the included studies' limitations, clinical implications, and identified gaps in evidence. These challenges are the implementation in routine care, individualized treatment options, adherence in unguided interventions, the minor role of health economic evaluations in German decision making, and methodological limitations.

4.6.1 Self-help IMIs in routine care

The European Federation of Psychologists' Association's (EFPA) E-Health Taskforce recommends the implementation of IMIs in routine care, given their great potential of improving mental health[63]. After establishing the intervention's efficacy, the effects of an implemented IMI are investigated (phase IV trials). If these results are promising, wide-scale adoption can follow. Thus, on account of their scalability and because they do not require the supervision of skilled mental care specialists, internet-based self-help interventions can extend treatment

coverage for those in need. Despite being promising, implementation poses major challenges for IMIs (e.g., diminishing treatment effects).

First, in practice, self-selected participants of controlled trials meet strict inclusion and exclusion criteria and may differ greatly from patients with mental disorders in routine care. These routine care patients are heterogenous, showing high levels of comorbidity, various symptom profiles and high disease burden.

Second, it is assumed that the research attention—which is absent under routine care condition—can serve as an adherence-promoting element. Self-help interventions are known to show lower adherence than guided interventions[188]. Previous findings support the impact of researcher attention and human support on adherence, indicating the presence of clinically relevant changes resulting from therapist-guided IMIs but showing only unclear evidence for the effectiveness of self-help IMIs under routine care conditions[202,203]. Thus, some form of adherence facilitation (e.g., automated feedback) and intervention process monitoring (e.g., automated reminders) is essential for self-help interventions in routine care[63].

Third, given their controlled nature, effects of RCTs are thought to be overestimated and to have limited generalizability, when compared with routine care conditions[204].

Fourth, recent meta-analytic evidence shows clinically relevant changes of internet-based (guided) CBT for depression and anxiety in routine care[205]. The results showed a moderate to high acceptability of interventions including uptake, adherence, and patient satisfaction, and only few negative effects. Nevertheless, due to the high heterogeneity of intervention methods and study contexts, only efficacious interventions should be chosen for routine care. Fifth, there exists a considerable gap in study quality and level of implementation between studies examining efficacy and those examining effectiveness. Highly efficacious interventions have repeatedly shown poor effectiveness in clinical practice when implemented[204]. This can be partially explained by barriers of implementation (e.g., time, costs, attitudes of professionals), and poor use of facilitating factors (e.g., knowledge of implementation). A systematic review presented a six cluster taxonomy that identified components that are necessary for improving the implementation of IMIs for mood disorders in routine practice: (1) the acceptance of IMIs to various stakeholders, (2) the appropriateness of the IMI in addressing the disorder, (3) the agency of implementing, delivering and receiving the IMI, (4) the availability and appropriateness of resources for implementing the IMI, (5) the processes for delivering IMIs, and (6) the leadership of processes involved in the implementation and delivery[206]. Each cluster contains important facilitators and barriers to implementation. For example, qualitative research on the participants' acceptance and satisfaction showed that location independence, positive

relationship to an e-coach, and target group specific adaption were the most common drivers for IMI use[207]. In contrast, qualitative research including general practitioners revealed that low knowledge about IMIs or patients' lack of familiarity with technology were hindering the referral of patients to blended internet-based psychotherapy[208]. Considering these clusters in the implementation design, execution and validation can improve implementation outcomes.

4.6.2 Adherence in unguided interventions

Adherence is defined as the sustained use of and engagement with digital interventions. Evidence suggests that low adherence and high attrition can accompany unguided interventions in pragmatic trials and routine care[63]. This can be explained in part by the fact that RCTs include structured elements and researcher attention (which promote adherence by securing participants' commitment), whereas unguided interventions do not[179]. Factors and strategies to improve adherence are of particular importance, as higher adherence is linked to larger treatment outcomes[209]. Adherence promoting elements can include increasing engagement, which is presumed to thereby improve adherence and treatment effects. There are many theoretical models that attempt to shed light on adherence, such as the Internet Intervention Model and The Unified Theory of Acceptance and Use of IT (UTAUT). All these comprehensive models share that the user's adherence to IMIs is explained by a combination of technological, environmental and individual factors, yet empirical evidence is lacking[210]. In the next section, I will discuss a selection of potential options to increase adherence for future research on internet-based self-help interventions.

Persuasive design is one approach for enhancing user engagement through adherence promoting factors. The persuasive system design (PSD) framework suggests that design principles can be categorized as (1) task support (e.g., the self-monitoring or tailoring of content helps to facilitate task completion), (2) dialogue support (e.g., that praise, rewards, appealing design, gamification help to enact target behavior), (3) system credibility support (e.g., the expertise and presentation of the research team), and (4) social support (e.g., to help user to motivate each other with a buddy system, social comparison)[211]. A recent review and meta-analysis evaluated the role of persuasive design in unguided iCBT for depression and anxiety. The researchers were able to demonstrate the effect of iCBTs on depression but not on anxiety disorder. Limitations included lack of reporting and evaluating of design elements, thus more research is needed[212].

For example, one adherence promoting method for iCBTs that has received increasing attention in recent years is that of gamification. Gamification is appealing and entertaining to many and represents another popular way to increase engagement, motivation, and adherence to digital interventions. Gamification—often interchangeably called serious gaming—refers to "the use of game design elements in non-game contexts[213]." Its principles include: a reasonable purpose, meaningful choices of users to reach the goal, reflecting individual player archetypes, feedback on how actions affect goal achievement, and visibility of progress. This five-factor gamification model can be used to improve user experience and enhance engagement with internet-based programs[214].

Implementing novel elements, like gamification, in a more widespread format could support researchers and policy makers in promoting unguided self-help interventions in real-world contexts.

4.6.3 Precision medicine in the treatment of SAD

The application of self-treatment methods is recommended as early as possible for patients with moderate SAD symptoms. For patients with severe SAD symptoms or patients who fail first-line and cost-effective interventions, individual and group therapy is advised[29]. For future research and treatment of severe SAD, the one-size-fits-all treatment approach is rejected and precision medicine or personalized or individualized treatments are recommended. Treatment should focus on the personalization of therapeutic strategies, taking a person's individual pathological presentation into account[29]. Individualization can be achieved through a combination of therapeutic strategies. New evidence, e.g., on personality profiles[215], avoidance of eye contact[216], and emotional reactivity, and regulation of social phobic patients can further improve the selection of suitable tools for an individualized SAD treatment. Thus, the "right" CBT technique can be used. For example, the social anxiety spectrum consists of an anxious ("social anxiety") and a phobic ("social phobia") dimension. The first is best treated by shifting attention to non-threatening stimuli and the second via traditional exposure therapy as patients avoid anxious stimuli. Other therapies such as mindfulness-based or acceptance-commitment therapy can be added when in line with the patient's needs. Given the flexibility of internet-based treatment, individualized adjustments including the addition or exchange of treatment modules can be performed relatively easily. Therefore, IMIs represent a promising treatment option in the light of treatment individualization.

4.6.4 Recommendations for future (clinical) research

This section discusses future recommendations for clinical research based on the limitations and clinical implications of Study One and Two and the previously discussed topics.

General recommendations:

- Head-to-head comparisons of IMIs versus usual care (e.g., blended approaches or F2F) should be used to mimic routine care conditions.
- Study durations should be extended to assess the long-term impact of (preventive) studies.
- The uptake and effectiveness of (unguided) IMIs should be examined after implementation and under routine care conditions.

Recommendations for Study One's unguided IMI targeting SAD in students:

- The student population should include students with subclinical SAD symptoms to examine the preventive effects of the IMI in patients at risk of developing SAD.
- Dismantling studies or additive designs should be used to evaluate treatment effects on fear of positive evaluation, of adherence promoting elements, and of individualized SAD treatment components.
- Confirmatory clinical trials on the efficacy of a variant of the IMI extended with adherence promoting elements, such as persuasive design, should be run under routine care conditions.

Recommendations for Study Two's presented iSMI targeting stressed employees:

- Confirmatory clinical trials for the iSMI should be run that reflect the general population, including persons with lower stress-levels, and a balanced sex ratio, without an elaborative inclusion process based on baseline symptom severity (similar to routine care).

4.6.5 Challenges in trial-based health economic evaluation

Several challenges can underlie methodological issues when conducting economic evaluations of digital health interventions. Researchers have posited that such issues relate to the product evolvement, the limited benefit assessment and the implementation level[187]. First, digital products need constant updates to ensure compatibility with operating systems or to include new research evidence. For this reason, flexible data collection and analytics tools are useful to assess sudden impacts on costs and effects. Second, intervention costs can be high if the IMI is newly developed, as they must recoup costs for research and development. Alternatively, they can be low as these costs (sunk costs) are not included in a merely modified IMI. Unfortunately, intervention costs are often reported insufficiently—this was also reaffirmed by our systematic review. Third, IMIs show low marginal costs (extra cost per unit produced) for maintenance and updates if scaled-up sufficiently. Despite this, scaling up does not inherently lead to improved cost-effectiveness. On the one hand, participants' costs used in trial-based economic evaluations may be overestimated when compared to an actual scaled up intervention's costs. On the other hand, inflated costs can be incurred if new digital systems need to be integrated (e.g., software for medical practice). Fourth, the benefit assessment of IMIs should include spill-over effects, such as efficiency gains based on improvements and increase in the quality of care (i.e., more resources for doctors allowing for more patient time). Additionally, effects that may arise outside of the healthcare system (such as patient empowerment and decreased travel expenses) are rarely included. Therefore, impact inventories should be expanded to include a wide range of health and non-health impacts are recommended.

4.6.6 The German reluctance to use health economic evaluations

As healthcare resources are limited, generic WTP thresholds are widely used as criteria when allocating scarce resources. New treatments are commonly assessed based on their therapeutic value to maximize resources (valued-based pricing). In Germany, the Institute for Quality and Efficiency in Health Care (IQWiG[217]) provides independent evidence-based expert opinions on, e.g., drugs, methods of diagnosis, and treatment guidelines. Moreover, the IQWiG provides lay understandable health information to citizens. The institute adheres to international guidelines on health economic evaluations proposed by the International Society for Pharmacoeconomics and Outcomes Research (ISPOR[218]), including their accepted methodological standards, i.e., perspective, time horizon, and statistical uncertainty of a cost-effectiveness

analysis (CEA). However, it rejects generic QALY-based WTP thresholds as they are not in line with value-based judgements as outlined in the legal requirements of the German Social Code Book V (Sozialgesetzbuch, SGB V[219]). The German regulatory framework is based upon the alignment of ethical and moral notions to meet individuals' rights. In needs-based economic evaluation, decision-making is centered on the idea of a medical need for coverage. This is in contrast to methods focusing on individual preferences (e.g., preference-based WTPs) or societal decision makers aiming to maximize health outcomes. For example, preference-based economic evaluations have been criticized for ranking resource allocations based on the preferences of affected individuals. Here the WTP is (1) dependent on the ability to pay and (2) does not reflect the greater disease burden and need for treatment present within disadvantaged population groups. This implies that for disorders with limited evidence for treatment efficacy, no treatment might be offered due to missing maximization potential, such as not meeting the cost threshold[220].

In the United Kingdom, the NICE applies a generic threshold of £20,000—£30,000 per additional QALY gained for the reimbursement of a new treatment. However, the IQWiG uses indication-specific thresholds based on the efficiency frontier (EF) approach, a recently developed method[221]. This approach plots all treatments for the indication, depicting costs on the horizontal axes and health effects (benefits) on the vertical axis. In this plot, a curve fitting the most efficient interventions form the EF. The cost-effectiveness of this frontier represented by the linearly interpolated incline of the last curve segment reflects the threshold a new intervention must meet or exceed. Essentially, IQWiG's "marginal rule" does not allow for direct comparison between therapeutic areas while the NICEs "average rule" compares across therapeutic areas[222]. Overall, CEAs are not needed to receive a market authorization for new drugs[223]. The German Act on the Reform of the Market for Medicinal Products (2011, Arzneimittelmarktneuordnungsgesetz, AMNOG) allows pharmaceutical manufacturers to negotiate prices for new drugs with the SHI grounded on early benefit assessments. Thus, the IQWiG is rarely commissioned to conduct health economic evaluations and only very few ICER thresholds of therapeutic areas are available.

The European Commission stressed that different methodologies in health economic evaluation and national procedures of HTA lead to redundancies and different market access thresholds for treatment across Europe[224]. In Germany, the IQWiG conducts HTA when a suggested treatment is relevant based on, e.g., prevalence, disease burden, and interventions costs. These HTAs are aligned with international standards including the assessment of benefits and the harms, economic, ethical, social, legal, and organizational aspects of the

intervention[219]. The goal of IQWiG's HTA is empower citizens to make autonomous and competent decisions regarding the various treatment options. A HTA report is conducted by an external expert who applies suggested methods and is enriched by an IQWiG's editor's comment. The reports are provided to relevant institutions in the healthcare system to positively influence patient care and decisions in self-governing organizations and politics[219]. Even so, in practice they are rarely used.

Several underlying reasons have been proposed for why economic evaluations are not included in the German decision-making process. These include justifications on the basis of cultural, historical, and ethical aspects[223]. The reluctance to ration medical products and impose a fixed maximum WTP for an intervention is rooted in historical restrictions and discrimination under the Nazi regime. The German Ethics Council and SGB V agree that if a patient needs a treatment the patient shall receive it. The legal text of SGB V states that health economic evaluations provide information to assist the Federal Joint Committee ("Gemeinsamer Bundesausschuss") about the appropriateness and affordability of a price for a new drug.

Historically, the German healthcare budget was not fixed and the SHI's funds well filled. Thus, there was no need for decision-making processes guided by health economic evaluations, and they were rarely used. Today the SHI is facing the highest financial deficits since 2003[225] due to consequences of the COVID-19 pandemic and the implementation of new laws. The pandemic, associated with an increase in morbidity and mortality rates, led to a sharp increase of costs for the German healthcare system. These costs further highlight the need for cost-effectiveness considerations.

Another reason for elevated costs for the healthcare system is illustrated by the DiGA market access approach. Although, the number of DiGAs greatly increased because of the relatively low standards that must be met for reimbursement (e.g., no standard care comparator needs to be used in trials), there exists no pricing regulation. In the first year of reimbursement, manufacturers can set their prices relatively freely. Only afterwards do the GKV-SV and the manufacturer negotiate the price for a DiGA. Thus, the GKV-SV has publicly called for the restriction of free pricing to reduce costs. As a result, an evidence-based approach to value-based DiGA pricing[226] has been developed to restrict pricing. This includes a comparison of the average cost-effectiveness of DiGAs with other reimbursable services in the therapeutic area (i.e., a price anchor such as F2F psychotherapy).

One question has not been answered yet: how can our studies' results influence German decision-making? In general, evidence on cost-effectiveness underpins the adoption of a new treatment or drug (e.g., of a DiGA application). Our studies include not only generic

measures (e.g., QALY) but also disease-specific outcome measures that are favored in Germany. Reusing existing evidence is preferable to the costs and time required to conduct contemporary economic evaluations using the EF approach. Thus, given the current financial pressure on the SHIs, our studies provide highly necessary information on how to allocate scarce resources. Such considerations may help promote the role of health economic evaluations in future research and decision-making.

4.6.7 Recommendations for future research on health economic evaluations

Below, short, future recommendations derived from the limitations and clinical implications of Study Three, the cost-effectiveness analyses of Study One and Two, and the topics discussed above are provided.

<u>General recommendations for conducting health economic evaluations alongside a clinical trial:</u>

- Trials should adhere to economic evaluation guidelines (ISPOR[227], CHEERS[218]) and quality checklists (RoB[142], Drummond[82], CHEC[228]) to minimize bias and improve study quality.
- Trials should include standard care comparators (e.g., F2F, other active control conditions) to mimic effects under routine conditions.
- Trials on IMIs should target under-represented and under-researched disorders to extend the evidence-base for the cost-effectiveness of IMIs.
- Trials should be designed with longer time horizons to allow for the better capture of long-term benefits and costs, e.g., productivity losses in preventive interventions, and resulting cost-effectiveness estimates.
- Trials should report intervention costs in detail (including development, hosting, maintenance).
- Where feasible (e.g., difficulty of recruiting enough patients), trials should be powered to detect differences in costs.
- Non-inferiority trials should be conducted to quantify the difference in effects and costs, e.g., between two active treatments, or between unguided self-help IMI vs. other guidance formats.
- Confirmatory trials are required to validate our studies health economic evaluations' results for both SAD and iSMI at the workplace.

Recommendations for decision makers in mental health care:

- Scientific and public discussions on economic considerations and evaluations are essential to educate and empower policy makers to make informed decisions on IMIs.
- Costs and treatment effects must be evaluated within and outside of the healthcare system to quantify the full impact of a treatment on society.
- Together with cost-effectiveness, decision makers should consider the target population, the overall symptom severity, the disease course, and the IMI's setting.
- Modeling studies, or a combination of individual patient-level data based on several RCTs, can address ethical aspects, disease burden, or bigger sample sizes that cannot be observed otherwise.

Recommendations for the broader health economic perspective:

- The harmonization of health economic standards and HTA standards can increase market access and the standardization of treatment access across Europe.
- More economic evaluations of IMIs in different economic and health care settings across the globe, especially in low- and middle-income countries, are needed.

While this thesis discusses many limitations, challenges, and future directions for IMIs, some aspects could not be addressed. These include data security, publication bias, patient safety, negative treatment effects, predispositions and characteristics of patients related to treatment effects, low health literacy, reasons for premature treatment discontinuation[229], user experience, and engagement.

4.7 Conclusion

In summary, Study One has shown that the presented unguided internet- and mobile-based intervention was effective in treating university students with social anxiety disorder. Moreover, the intervention represented a good value for money and was able to maintain the effects in the long-term at 6 months follow-up. The German SAD treatment guidelines recommend IMIs as a complement to F2F treatment or a means to bridge waiting times. However, our results support the emerging evidence that (guided) IMIs for SAD are a viable first-line treatment option, as already practiced in other countries (e.g., New Zealand, Australia). I suggest implementing this low-threshold and cost-effective intervention as part of a student healthcare management at a university.

Study Two provided evidence that a guided internet-based stress management intervention in employees with elevated stress level represents a good value for money. The results showed that merely the inclusion of costs relevant to the employer, such as productivity losses, already yielded favorable probabilities of its cost-effectiveness and a positive financial return. Likewise, taking a societal perspective led to a promising likelihood of the intervention being cost-effective compared to a waitlist control group. Given the high efficacy and cost-effectiveness, this iSMI represents a promising means of improving mental health at the workplace. Implementing this iSMI as part of occupational health care or from the employer's perspective seems beneficial.

Study Three expanded the limited evidence on the cost-effectiveness of IMIs for mental disorders and symptoms. Its results showed that guided IMIs targeting depression and anxiety are likely to be cost-effective and hence should be recommended to decision makers as a viable treatment option. Yet, findings were limited by high heterogeneity due to different costing methods, designs, comparators, and outcomes used. Given these limitations, more research in under-researched disorders, unguided (preventive) IMIs, and active and usual care comparators with long follow-up periods are needed to make further conclusions.

5. References

1. World Health Organization. *Comprehensive mental health action plan 2013–2030*. (2021).
2. GBD 2019 Mental Disorders Collaborators. Global, regional, and national burden of 12 mental disorders in 204 countries and territories, 1990–2019: a systematic analysis for the Global Burden of Disease Study 2019. *The Lancet Psychiatry* **9**, 137–150 (2022).
3. Rehm, J. & Shield, K. D. Global Burden of Disease and the Impact of Mental and Addictive Disorders. *Curr Psychiatry Rep* **21**, (2019).
4. Hasin, D. S. *et al.* Epidemiology of Adult DSM-5 Major Depressive Disorder and Its Specifiers in the United States. *JAMA Psychiatry* **75**, 336–346 (2018).
5. Kessler, R. C., Petukhova, M., Sampson, N. A., Zaslavsky, A. M. & Wittchen, H. U. Twelve-month and lifetime prevalence and lifetime morbid risk of anxiety and mood disorders in the United States. *Int. J. Methods Psychiatr. Res.* **21**, 169–184 (2012).
6. Hohls, J. K., König, H. H., Quirke, E. & Hajek, A. Anxiety, depression and quality of life—a systematic review of evidence from longitudinal observational studies. *Int. J. Environ. Res. Public Health* **18**, 12022 (2021).
7. Walker, E. R., McGee, R. E. & Druss, B. G. Mortality in mental disorders and global disease burden implications a systematic review and meta-analysis. *JAMA Psychiatry* **72**, 334–341 (2015).
8. McGrath, J. J. *et al.* Comorbidity within mental disorders: a comprehensive analysis based on 145 990 survey respondents from 27 countries. *Epidemiol. Psychiatr. Sci.* **29**, (2020).
9. Iacovides, A. & Siamouli, M. Comorbid mental and somatic disorders: an epidemiological perspective. *Curr. Opin. Psychiatry* **21**, 417–421 (2008).
10. Sartorius, N. Depression and diabetes. *Dialogues Clin. Neurosci.* **20**, 47–52 (2018).
11. Santomauro, D. F. *et al.* Global prevalence and burden of depressive and anxiety disorders in 204 countries and territories in 2020 due to the COVID-19 pandemic. *Lancet* **398**, 1700–1712 (2021).
12. Salari, N. *et al.* Prevalence of stress, anxiety, depression among the general population during the COVID-19 pandemic: A systematic review and meta-analysis. *Global. Health* **16**, 1–11 (2020).
13. Ettman, C. K. *et al.* Prevalence of Depression Symptoms in US Adults Before and During

the COVID-19 Pandemic. *JAMA Netw. open* **3**, (2020).

14. Robinson, E., Sutin, A. R., Daly, M. & Jones, A. A systematic review and meta-analysis of longitudinal cohort studies comparing mental health before versus during the COVID-19 pandemic in 2020. *J. Affect. Disord.* **296**, 567–576 (2022).
15. Daly, M. & Robinson, E. Depression and anxiety during COVID-19. *Lancet* **399**, 518 (2022).
16. Schofield, D. J. *et al.* The personal and national costs of mental health conditions: impacts on income, taxes, government support payments due to lost labour force participation. *BMC Psychiatry* **11**, (2011).
17. Trautmann, S., Rehm, J. & Wittchen, H. U. The economic costs of mental disorders: Do our societies react appropriately to the burden of mental disorders? *EMBO Rep.* **17**, 1245–1249 (2016).
18. Yousefi, M., Assari Arani, A., Sahabi, B., Kazemnejad, A. & Fazaeli, S. Household Health Costs: Direct, Indirect and Intangible. *Iran. J. Public Health* **43**, 202 (2014).
19. Gustavsson, A. *et al.* Cost of disorders of the brain in Europe 2010. *Eur. Neuropsychopharmacol.* **21**, 718–779 (2011).
20. Bloom, D. E. *et al. The global economic burden of non-communicable diseases (Working Paper Series)*. (Harvard School of Public Health and World Economic Forum, 2011).
21. Chisholm, D. *et al.* Scaling-up treatment of depression and anxiety: A global return on investment analysis. *The Lancet Psychiatry* **3**, 415–424 (2016).
22. Stein, D. J. *et al.* The cross-national epidemiology of social anxiety disorder: Data from the World Mental Health Survey Initiative. *BMC Med.* **15**, 1–21 (2017).
23. Niermann, H. C. M. *et al.* Anxiety disorders among adolescents and young adults: Prevalence and mental health care service utilization in a regional epidemiological study in Germany. *J. Anxiety Disord.* **83**, 102453 (2021).
24. American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders DSM-V (5th Edition)*. (American Psychiatric Association, 2013). doi:10.1176/APPI.BOOKS.9780890425596.
25. Spence, S. H. & Rapee, R. M. The etiology of social anxiety disorder: An evidence-based model. *Behav. Res. Ther.* **86**, 50–67 (2016).
26. Zimmermann, M., Chong, A. K., Vechiu, C. & Papa, A. Modifiable risk and protective factors for anxiety disorders among adults: A systematic review. *Psychiatry Res.* **285**, 112705 (2020).
27. Koyuncu, A., İnce, E., Ertekin, E. & Tükel, R. Comorbidity in social anxiety disorder:

diagnostic and therapeutic challenges. *Drugs Context* **8**, (2019).

28. Allen, D., Hines, E. W., Pazdernik, V., Konecny, L. T. & Breitenbach, E. Four-year review of presenteeism data among employees of a large United States health care system: A retrospective prevalence study. *Hum. Resour. Health* **16**, 1–10 (2018).
29. Pelissolo, A., Abou Kassm, S. & Delhay, L. Therapeutic strategies for social anxiety disorder: where are we now? *Expert Rev. Neurother.* **19**, 1179–1189 (2019).
30. Mayo-Wilson, E. *et al.* Psychological and pharmacological interventions for social anxiety disorder in adults: a systematic review and network meta-analysis. *The Lancet Psychiatry* **1**, 368–376 (2014).
31. Goetter, E. M. E. *et al.* Barriers to mental health treatment among individuals with social anxiety disorder and generalized anxiety disorder. *Psychol. Serv.* **17**, 5–12 (2018).
32. Papadimitriou, G. The 'Biopsychosocial Model': 40 years of application in Psychiatry. *Psychiatrike* **28**, 107–110 (2017).
33. Nolen-Hoeksema, S. *Abnormal Psychology: Eight Edition*. (Mc Graw Hill Education, 2020).
34. Schiele, M. A. *et al.* Extending the vulnerability-stress model of mental disorders: three-dimensional NPSR1 × environment × coping interaction study in anxiety. *Br. J. Psychiatry* **217**, 645–650 (2020).
35. Turner, A. I. *et al.* Psychological stress reactivity and future health and disease outcomes: A systematic review of prospective evidence. *Psychoneuroendocrinology* **114**, 104599 (2020).
36. Yang, L. *et al.* The Effects of Psychological Stress on Depression. *Curr. Neuropharmacol.* **13**, 494–504 (2015).
37. Kalmbach, D. A., Anderson, J. R. & Drake, C. L. The impact of stress on sleep: Pathogenic sleep reactivity as a vulnerability to insomnia and circadian disorders. *J. Sleep Res.* **27**, e12710 (2018).
38. Wirtz, P. H. & von Känel, R. Psychological Stress, Inflammation, and Coronary Heart Disease. *Curr. Cardiol. Rep.* **19**, 1–10 (2017).
39. Siegrist, J. Adverse health effects of high-effort/low-reward conditions. *J. Occup. Health Psychol.* **1**, 27–41 (1996).
40. Karasek, R. A. Job Demands, Job Decision Latitude, and Mental Strain: Implications for Job Redesign. *Adm. Sci. Q.* **24**, 285 (1979).
41. Lazarus, R. & Folkman, S. *Stress, appraisal, and coping*. (Springer Publishing Co, 1984).
42. Holman, D., Johnson, S. & O'Connor, E. Stress Management Interventions : Improving

Subjective Psychological Well-Being in the Workplace. in *Handbook of well-being* (DEF Publishers, 2018).

43. Kaluza, G. Stress und Stressbewältigung. *Erfahrungsheilkunde* **63**, 261–267 (2014).
44. Bhui, K. S., Dinos, S., Stansfeld, S. A. & White, P. D. A synthesis of the evidence for managing stress at work: a review of the reviews reporting on anxiety, depression, and absenteeism. *J. Environ. Public Health* **2012**, (2012).
45. van der Klink, J. J., Blonk, R. W., Schene, A. H. & van Dijk, F. J. The benefits of interventions for work-related stress. *Am. J. Public Health* **91**, 270–6 (2001).
46. Chanen, A. M. & Nicol, K. Five failures and five challenges for prevention and early intervention for personality disorder. *Curr. Opin. Psychol.* **37**, 134–138 (2021).
47. Stagnaro, J. C. *et al.* Delays in making initial treatment contact after the first onset of mental health disorders in the Argentinean Study of Mental Health Epidemiology. *Epidemiol. Psychiatr. Sci.* **28**, 240–250 (2019).
48. Cuijpers, P. *et al.* Psychological treatment of generalized anxiety disorder: a meta-analysis. *Clin. Psychol. Rev.* **34**, 130–140 (2014).
49. Zhou, X. *et al.* Comparative efficacy and acceptability of antidepressants, psychotherapies, and their combination for acute treatment of children and adolescents with depressive disorder: a systematic review and network meta-analysis. *The Lancet Psychiatry* **7**, 581–601 (2020).
50. Cuijpers, P. *et al.* Psychological treatment of depression in institutional settings: A meta-analytic review. *J. Affect. Disord.* **286**, 340–350 (2021).
51. Bandelow, B. *et al.* Efficacy of treatments for anxiety disorders: a meta-analysis. *Int. Clin. Psychopharmacol.* **30**, 183–192 (2015).
52. Jenkins, R., Baingana, F., Ahmad, R., McDaid, D. & Atun, R. Health system challenges and solutions to improving mental health outcomes. *Ment. Health Fam. Med.* **8**, 119 (2011).
53. Mack, S. *et al.* Self-reported utilization of mental health services in the adult German population - evidence for unmet needs? Results of the DEGS1-Mental health module (DEGS1-MH). *Int. J. Methods Psychiatr. Res.* **23**, 289–303 (2014).
54. Andrade, L. H. *et al.* Barriers to mental health treatment: results from the WHO World Mental Health surveys. *Psychol Med* **44**, 1303–1317 (2014).
55. Mueller-Stierlin, A. S. *et al.* The Cost-Effectiveness Analysis of an Integrated Mental Health Care Programme in Germany. *Int. J. Environ. Res. Public Health* **19**, 6814 (2022).
56. Dell'Osso, B., Glick, I. D., Baldwin, D. S. & Altamura, A. C. Can Long-Term Outcomes Be Improved by Shortening the Duration of Untreated Illness in Psychiatric Disorders? A

Conceptual Framework. *Psychopathology* **46**, 14–21 (2013).

57. Doering, L. V. *et al.* Persistent comorbid symptoms of depression and anxiety predict mortality in heart disease. *Int. J. Cardiol.* **145**, 188–192 (2010).
58. Hilty, D. M., Chan, S., Hwang, T., Wong, A. & Bauer, A. M. Advances in mobile mental health: opportunities and implications for the spectrum of e-mental health services. *mHealth* **3**, 34–34 (2017).
59. Lattie, E. G. *et al.* Digital mental health interventions for depression, anxiety and enhancement of psychological well-being among college students: Systematic review. *J. Med. Internet Res.* **21**, e12869 (2019).
60. Treanor, C. J., Kouvonen, A., Lallukka, T. & Donnelly, M. Acceptability of computerized cognitive behavioral therapy for adults: Umbrella review. *JMIR Ment. Heal.* **8**, e23091 (2021).
61. Batterham, P. J. *et al.* Factors associated with engagement in online self-help programs among people with suicidal thoughts. *J. Affect. Disord.* **265**, 402–409 (2020).
62. Ebert, D. D., Harrer, M., Apolinário-Hagen, J. & Baumeister, H. Digital Interventions for Mental Disorders: Key Features, Efficacy, and Potential for Artificial Intelligence Applications. in *Frontiers in Psychiatry. Advances in Experimental Medicine and Biology* (ed. Kim, Y.-K.) 583–627 (Adv Exp Med Biol, 2019). doi:10.1007/978-981-32-9721-0_29.
63. Ebert, D. D. *et al.* Internet- and Mobile-Based Psychological Interventions: Applications, Efficacy, and Potential for Improving Mental Health. A report of the EFPA E-Health Taskforce. *Eur. Psychol.* **23**, 167–187 (2018).
64. Andersson, G., Carlbring, P., Titov, N. & Lindefors, N. Internet Interventions for Adults with Anxiety and Mood Disorders : A Narrative Umbrella Review of Recent Meta-Analyses. *Can. J. Psychiatry* **64**, 465–470 (2019).
65. Andrews, G. *et al.* Computer therapy for the anxiety and depression disorders is effective, acceptable and practical health care: an updated meta-analysis. *J. Anxiety Disord.* **55**, 70–78 (2018).
66. Andersson, G., Rozental, A., Shafran, R. & Carlbring, P. Long-term effects of internet-supported cognitive behaviour therapy. *Expert Rev. Neurother.* **18**, 21–28 (2018).
67. Kampmann, I. L., Emmelkamp, P. M. G. & Morina, N. Meta-analysis of technology-assisted interventions for social anxiety disorder. *J. Anxiety Disord.* **42**, 71–84 (2016).
68. Berger, T. *et al.* Internet-based treatment of social phobia: A randomized controlled trial comparing unguided with two types of guided self-help. *Behav. Res. Ther.* **49**, 158–169 (2011).

69. Botella, C. *et al.* An Internet-Based Self-Help Treatment for Fear of Public Speaking : A Controlled Trial. *Cyberpsychology, Behav. Soc. Netw.* **13**, (2010).
70. Furmark, T. *et al.* Guided and unguided self-help for social anxiety disorder: randomised controlled trial. *Br. J. Psychiatry* **195**, 440–447 (2009).
71. Gallego, M. J., Emmelkamp, G., Maria, P., Kooij, M. van der & Mees, H. The effects of a Dutch version of an Internet-based treatment program for fear of public speaking: A controlled study. *Int. J. Clin. Heal. Psychol.* **11**, 459–472 (2011).
72. Lopez, G. C., Botella, C., Quero, S., Gomez, A. R. & Baños, R. Telepsychology program to treat public-speaking anxiety among the Mexican population. *Psicol. Iberoam.* **22**, 45–54 (2014).
73. Titov, N., Andrews, G., Choi, I., Schwencke, G. & Mahoney, A. Shyness 3: Randomized controlled trial of guided versus unguided Internet-based CBT for social phobia. *Aust. N. Z. J. Psychiatry* **42**, 1030–1040 (2008).
74. Titov, N., Andrews, G., Choi, I., Schwencke, G. & Johnston, L. Randomized Controlled Trial of Web-Based Treatment of Social Phobia Without Clinician Guidance. *Aust. New Zeal. J. Psychiatry* **43**, 913–919 (2009).
75. Titov, N. *et al.* Randomized Controlled Trial of Internet Cognitive Behavioural Treatment for Social Phobia with and Without Motivational Enhancement Strategies. *Aust. New Zeal. J. Psychiatry* **44**, 938–945 (2010).
76. Tillfors, M. *et al.* Treating university students with social phobia and public speaking fears: internet delivered self-help with or without live group exposure sessions. *Depress. Anxiety* **25**, 708–717 (2008).
77. American Psychological Association. Guidelines for prevention in psychology. *Am. Psychol.* **69**, 285–296 (2014).
78. Sander, L. *et al.* Effectiveness of Internet-Based Interventions for the Prevention of Mental Disorders: A Systematic Review and Meta-Analysis. *JMIR Ment Heal.* **3**, 1–20 (2016).
79. Gordon, R., Steinberg, J. A. & Silverman, M. M. An operational classification of disease prevention. W: Preventing Mental Disorders. *Rockville, MD US Dep. Heal. Hum. Serv.* (1987).
80. van Doorn, M. *et al.* Online Indicated Preventive Mental Health Interventions for Youth: A Scoping Review. *Front. Psychiatry* **12**, 580843 (2021).
81. Heber, E. *et al.* The Benefit of Web- and Computer-Based Interventions for Stress: A Systematic Review and Meta-Analysis. *J. Med. Internet Res.* **19**, e5774 (2017).

82. Drummond, M., Sculpher, M. J., Claxton, K., Stoddart, G. L. & Torrance, G. W. *Methods for the Economic Evaluation of Health Care Programmes*. (Oxford University Press, 2015).
83. Brennan, A. & Akehurst, R. Modelling in health economic evaluation: What is its place? What is its value? *Pharmacoeconomics* **17**, 445–459 (2000).
84. Arnberg, F. K., Linton, S. J., Hultcrantz, M., Heintz, E. & Jonsson, U. Internet-delivered psychological treatments for mood and anxiety disorders: a systematic review of their efficacy, safety, and cost-effectiveness. *PLoS One* **9**, 1–13 (2014).
85. Donker, T. *et al.* Economic evaluations of Internet interventions for mental health: a systematic review. *Psychol. Med.* **45**, 3357–3376 (2015).
86. Ophuis, R. H. *et al.* Cost-effectiveness of interventions for treating anxiety disorders: A systematic review. *J. Affect. Disord.* **21**, 1–13 (2017).
87. Paganini, S., Teigelkötter, W., Buntrock, C. & Baumeister, H. Economic evaluations of internet- and mobile-based interventions for the treatment and prevention of depression: A systematic review. *J. Affect. Disord.* **225**, 733–755 (2018).
88. Hedman, E. *et al.* Cost-effectiveness of Internet-based cognitive behavior therapy vs. cognitive behavioral group therapy for social anxiety disorder: Results from a randomized controlled trial. *Behav. Res. Ther.* **49**, 729–736 (2011).
89. Nordgren, L. B. *et al.* Effectiveness and cost-effectiveness of individually tailored Internet-delivered cognitive behavior therapy for anxiety disorders in a primary care population: a randomized controlled trial. *Behav Res Ther* **59**, 1–11 (2014).
90. Titov, N., Andrews, G., Johnston, L., Schwencke, G. & Choi, I. Shyness programme: longer term benefits, cost-effectiveness, and acceptability. *Aust. N. Z. J. Psychiatry* **43**, 36–44 (2009).
91. Harvard Medical School. The WHO World Mental Health International College Student (WMH-ICS) Initiative. https://www.hcp.med.harvard.edu/wmh/college_student_survey.php (2022).
92. Kählke, F., Küchler, A.-M., Baumeister, H. & Ebert, D. D. StudiCare erfolgreich und gesund studieren-ein umfassendes deutsches und internationales Projekt zur Förderung der psychischen Gesundheit von Studierenden. *Fachzeitschrift für Onlineberatung und Comput. Kommun.* **15**, 133–156 (2019).
93. Heinrichs, N. *et al.* Validität und Reliabilität der Social Interaction Anxiety Scale (SIAS) und der Social Phobia Scale (SPS). *Verhaltenstherapie* **12**, 26–35 (2002).
94. Stangier, U., Heidenreich, T., Berardi, A., Golbs, U. & Hoyer, J. Die Erfassung sozialer

Phobie durch die Social Interaction Anxiety Scale (SIAS) und die Social Phobia Scale (SPS). *Z. Klin. Psychol. Psychother.* **28**, 28–36 (1999).

95. Kählke, F. *et al.* Efficacy and cost-effectiveness of an unguided, internet- and mobile-based self-help intervention for social anxiety disorder in university students: protocol of a randomized controlled trial. *BMC Psychiatry* **19**, e1766 (2019).
96. Clark, D. & Wells, A. *A cognitive model of social phobia*. (Guilford Press, 1995).
97. Boettcher, J., Berger, T. & Renneberg, B. Does a Pre-Treatment Diagnostic Interview Affect the Outcome of Internet-Based Self-Help for Social Anxiety Disorder? A Randomized Controlled Trial. *Behav. Cogn. Psychother.* **40**, 513–528 (2012).
98. Berger, T., Hohl, E., Berger, T., Hohl, E. & Caspar, F. Internetbasierte Therapie der sozialen Phobie : Ergebnisse einer. *Z. Klin. Psychol. Psychother.* **39**, 217–221 (2010).
99. Schulz, A., Stolz, T. & Berger, T. Internet-based individually versus group guided self-help treatment for social anxiety disorder: protocol of a randomized controlled trial. *BMC Psychiatry* **14**, 1–8 (2014).
100. Questback GmbH. Unipark. *EFS Survey* (2016).
101. Wittchen, H.-U., Wunderlich, U., Gruschwitz, S. & Zaudig, M. *SKID I. Strukturiertes Klinisches Interview für DSM-IV. Achse I: Psychische Störungen. Interviewheft und Beurteilungsheft. Eine deutschsprachige, erweiterte Bearb. d. amerikanischen Originalversion des SKID I*. (Hogrefe, 1997).
102. Horowitz, L. *et al.* Inventory of interpersonal problems: Psychometric properties and clinical applications. *J. Consult. Clin. Psychol.* **56**, 885–892 (1988).
103. Kühner, C., Bürger, C., Keller, F. & Hautzinger, M. Reliabilität und validität des revidierten Beck- Depressionsinventars (BDI-II). Befunde aus deutschsprachigen stichproben. *Nervenarzt* **78**, 651–656 (2007).
104. Weeks, J. W., Heimberg, R. G., Rodebaugh, T. L., Goldin, P. R. & Gross, J. J. Psychometric evaluation of the Fear of Positive Evaluation Scale in patients with social anxiety disorder. *Psychol. Assess.* **24**, 301–312 (2012).
105. Spitzer, C. *et al.* [The short version of the Brief Symptom Inventory (BSI -18): preliminary psychometric properties of the German translation]. *Fortschr. Neurol. Psychiatr.* **79**, 517–523 (2011).
106. Devilly, G. J. & Borkovec, T. D. Psychometric properties of the credibility/expectancy questionnaire. *J. Behav. Ther. Exp. Psychiatry* **31**, 73–86 (2000).
107. Schmidt, J., Lamprecht, F. & Wittmann, W. W. Zufriedenheit mit der stationären Versorgung. Entwicklung eines Fragebogens und erste Validitätsuntersuchungen. *PPmP*

Psychother. Psychosom. Medizinische Psychol. **39**, 248–255 (1989).

108. Richardson, J., Iezzi, A., Khan, M. A. & Maxwell, A. Validity and Reliability of the Assessment of Quality of Life (AQoL)-8D Multi-Attribute Utility Instrument. *Patient - Patient-Centered Outcomes Res.* **7**, 85–96 (2014).
109. Bouwmans, C. *et al.* Feasibility, reliability and validity of a questionnaire on healthcare consumption and productivity loss in patients with a psychiatric disorder (TiC-P). *BMC Health Serv. Res.* **13**, 217 (2013).
110. Matthews, J. N., Altman, D. G., Campbell, M. J. & Royston, P. Analysis of serial measurements in medical research. *BMJ* **300**, 230–235 (1990).
111. Shemilt, I., Thomas, J. & Morciano, M. A web-based tool for adjusting costs to a specific target currency and price year. *Evid. Policy* **6**, 51–59 (2010).
112. IBM Corp. IBM SPSS Statistics for Windows, Version 25.0. (2017).
113. StataCorp. Stata Statistical Software: Release 16. (2019).
114. Hout, B. A. Van, Al, M. J., Gordon, G. S. & Rutten, F. F. H. Costs, effects and C/E-ratios alongside a clinical trial. *Health Econ.* **3**, 309–319 (1994).
115. Briggs, A. H. & Gray, A. M. Handling uncertainty in economic evaluations of healthcare interventions. *BMJ* **319**, 635–8 (1999).
116. Willan, A. R., Briggs, A. H. & Hoch, J. S. Regression methods for covariate adjustment and subgroup analysis for non-censored cost-effectiveness data. *Health Econ.* **13**, 461–475 (2004).
117. Fenwick, E., O'Brien, B. & Briggs, A. Cost-effectiveness acceptability curves: facts, fallacies and frequently asked questions. *Health Econ.* **13**, 405–415 (2004).
118. Sonntag, M. *et al.* Reliability, validity and responsiveness of the EQ-5D in assessing and valuing health status in patients with social phobia. *Heal. Qual Life Outcomes* **11**, 215 (2013).
119. Heber, E. *et al.* Efficacy and cost-effectiveness of a web-based and mobile stress-management intervention for employees: design of a randomized controlled trial. *BMC Public Health* **13**, 655 (2013).
120. Leuphana Universität Lüneburg & Institut für Psychologie. GET.ON GesundheitsTraining.Online. https://geton-training.de/ (2020).
121. Cohen, S., Kamarck, T. & Mermelstein, R. A global measure of perceived stress. *J Heal. Soc Behav* **24**, 385 (1983).
122. Klein, E. M. *et al.* The German version of the Perceived Stress Scale - psychometric characteristics in a representative German community sample. *BMC Psychiatry* **16**, 159

(2016).

123. D'Zurilla, T. J. & Nezu, A. M. Problem-solving therapy. in *Handbook of cognitive-behavioral therapies* (ed. Dobson, K. S.) 197–225 (Guilford Press, 2010).
124. Berking, M. & Whitley, B. *Affect Regulation Training*. *Affect Regulation Training. A Practitioners' Manual* (Springer New York, 2014). doi:10.1007/978-1-4939-1022-9.
125. Radloff, L. S. The CES-D Scale: A Self-Report Depression Scale for Research in the General Population. *Appl. Psychol. Meas.* **1**, 385–401 (1977).
126. Hermann-Lingen, C., Buss, U. & Snaith, R. *Hospital Anxiety and Depression Scale - Deutsche Version (HADS-D)*. (Huber, Hans, 2011).
127. Ebert, D. D., Christ, O. & Berking, M. Entwicklung und Validierung eines Fragebogens zur emotionsspezifischen Selbsteinschätzung emotionaler Kompetenzen (SEK-ES). *Diagnostica* **59**, 17–32 (2013).
128. Schaufeli, W. & Bakker, A. *Utrecht Work Engagement Scale: Test Manual*. (The Netherlands Departmant of Psychology, Utrecht University, 2003).
129. Ware, J. E., Kosinski, M. & Keller, S. D. A 12-Item Short-Form Health Survey: Construction of Scales and Preliminary Tests of Reliability and Validity. *Med. Care* **34**, 220–233 (1996).
130. Osterhaus, J. T., Gutterman, D. L. & Plachetka, J. R. Healthcare resource and lost labour costs of migraine headache in the US. *Pharmacoeconomics* **2**, 67–76 (1992).
131. Heber, E., Lehr, D., Ebert, D. D., Berking, M. & Riper, H. Web-based and mobile stress management intervention for employees: results of a randomised controlled trial. *J Med Internet Res* **18**, e5112 (2016).
132. StataCorp. Stata Statistical Software: Release 14. (2013).
133. Kählke, F. *et al.* Economic Evaluation of an Internet-Based Stress Management Intervention Alongside a Randomized Controlled Trial. *JMIR Ment. Heal.* **6**, 1–13 (2019).
134. van Dongen, J. M. *et al.* Trial-Based Economic Evaluations in Occupational Health: Principles, Methods, and Recommendations. *J. Occup. Environ. Med.* **56**, 563–572 (2014).
135. Leigh, J. P. Expanding research on the economics of occupational health. *Scand. J. Work. Environ. Health* **32**, 1–4 (2006).
136. PROSPERO Registry. https://www.crd.york.ac.uk/PROSPERO/display_record.php?RecordID=93808 (2018).
137. Page, M. J. *et al.* The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. *Syst. Rev.* **10**, 1–11 (2021).
138. Husereau, D. *et al.* Consolidated health economic evaluation reporting standards 2022

(CHEERS 2022) statement: updated reporting guidance for health economic evaluations. *Int. J. Technol. Assess. Health Care* **38**, e13 (2022).

139. Organisation for Economic Co-operation and Development (OECD). *PPP and exchanges Rates*. https: //data.oecd.org/conversion/purchasing.power-parties-ppp.htm (2018).
140. Tate, D. F., Finkelstein, E. a, Khavjou, O. & Gustafson, A. Cost effectiveness of internet interventions: review and recommendations. *Ann. Behav. Med.* **38**, 40–5 (2009).
141. Evers, S., Goossens, M., de Vet, H., van Tulder, M. & Ament, A. Criteria list for assessment of methodological quality of economic evaluations: Consensus on Health Economic Criteria. *Int J Technol Assess Heal. Care* **21**, 240–245 (2005).
142. Higgins, J. P. & Altman, D. G. Assessing Risk of Bias in Included Studies. in *Cochrane Handbook for Systematic Reviews of Interventions* 187–241 (John Wiley & Sons, Ltd, 2008). doi:10.1002/9780470712184.ch8.
143. Viswanathan, M. *et al.* Recommendations for assessing the risk of bias in systematic reviews of health-care interventions. *J. Clin. Epidemiol.* **97**, 26–34 (2018).
144. Kählke, F. *et al.* Long-term Outcomes and Cost-Effectiveness of an Internet-Based Self-Help Intervention for Social Anxiety Disorder in University Students: A Randomized Controlled Trial. *Submitt. to NPJ Hum. Behav.* (2022).
145. Guo, S. *et al.* The efficacy of internet-based cognitive behavioural therapy for social anxiety disorder: A systematic review and meta-analysis. *Clin. Psychol. Psychother.* **28**, 656–668 (2020).
146. Dear, B. F. *et al.* Transdiagnostic versus disorder-specific and clinician-guided versus self-guided internet-delivered treatment for Social Anxiety Disorder and comorbid disorders: A randomized controlled trial. *J. Anxiety Disord.* **42**, 30–44 (2016).
147. Powell, J. *et al.* Effectiveness and Cost-Effectiveness of a Self-Guided Internet Intervention for Social Anxiety Symptoms in a General Population Sample: Randomized Controlled Trial. *J. Med. Internet Res.* **22**, e16804 (2020).
148. Reins, J. A. *et al.* Efficacy and Moderators of Internet-Based Interventions in Adults with Subthreshold Depression: An Individual Participant Data Meta-Analysis of Randomized Controlled Trials. *Psychother. Psychosom.* **90**, 94–106 (2021).
149. McCall, H. C., Richardson, C. G., Helgadottir, F. D. & Chen, F. S. Evaluating a Web-Based Social Anxiety Intervention Among University Students: Randomized Controlled Trial. *J. Med. Internet Res.* **20**, e8630 (2018).
150. Hedman, E. *et al.* Clinical effectiveness and cost-effectiveness of Internet- vs. group-based cognitive behavior therapy for social anxiety disorder: 4-year follow-up of a

randomized trial. *Behav. Res. Ther.* **59**, 20–29 (2014).

151. Heber, E., Lehr, D., Ebert, D. D., Berking, M. & Riper, H. Web-Based and Mobile Stress Management Intervention for Employees: A Randomized Controlled Trial. *J Med Internet Res* **18**, e5112 (2016).
152. Pieper, C., Schröer, S. & Eilerts, A. L. Evidence of workplace interventions-A systematic review of systematic reviews. *Int. J. Environ. Res. Public Health* **16**, 3553 (2019).
153. Estevez Cores, S., Sayed, A. A., Tracy, D. K. & Kempton, M. J. Individual-focused occupational health interventions: A meta-analysis of randomized controlled trials. *J. Occup. Health Psychol.* **26**, 189–203 (2021).
154. Svärdman, F., Sjöwall, D. & Lindsäter, E. Internet-delivered cognitive behavioral interventions to reduce elevated stress: A systematic review and meta-analysis. *Internet Interv.* **29**, 100553 (2022).
155. Le, L. K.-D. *et al.* Cost-effectiveness evidence of mental health prevention and promotion interventions: A systematic review of economic evaluationsAU : *PLoS Med.* **18**, e1003606 (2021).
156. Thiart, H. *et al.* Internet-Based Cognitive Behavioral Therapy for Insomnia: A Health Economic Evaluation. *Sleep* **39**, 1769–1778 (2016).
157. Geraedts, A. S. *et al.* Economic evaluation of a web-based guided self-help intervention for employees with depressive symptoms: Results of a randomized controlled trial. *J. Occup. Environ. Med.* **57**, 666–675 (2015).
158. Lindsäter, E. *et al.* Cost-Effectiveness of Therapist-Guided Internet-Based Cognitive Behavioral Therapy for Stress-Related Disorders: Secondary Analysis of a Randomized Controlled Trial. *J. Med. Internet Res.* **21**, e14675 (2019).
159. Hedman, E., Andersson, E., Ljotsson, B., Axelsson, E. & Lekander, M. Cost effectiveness of internet-based cognitive behaviour therapy and behavioural stress management for severe health anxiety. *BMJ Open* **6**, 1–8 (2016).
160. Mitchell, L. M., Joshi, U., Patel, V., Lu, C. & Naslund, J. A. Economic Evaluations of Internet-Based Psychological Interventions for Anxiety Disorders and Depression: A Systematic Review. *J. Affect. Disord.* **284**, 157–182 (2021).
161. Conejo-Cerón, S. *et al.* Health-economic evaluation of psychological interventions for depression prevention: Systematic review. *Clin. Psychol. Rev.* **88**, 102064 (2021).
162. Le, L. K.-D., Hay, P. & Mihalopoulos, C. A systematic review of cost-effectiveness studies of prevention and treatment for eating disorders. *Aust. N. Z. J. Psychiatry* **52**, 328–338 (2018).

163. Buntrock, C., Kählke, F., Smit, F. & Ebert, D. D. A systematic review of trial-based economic evaluations of internet- and mobile-based interventions for substance use disorders. *Eur. J. Public Health* **31**, i19–i28 (2021).
164. Mutyambizi-Mafunda, V. *et al.* Economic Evaluation of Psychological Treatments for Common Mental Disorders in Low- and Middle-Income Countries: A Systematic Review. *Health Policy Plan.* czac069 (2022).
165. Sung, J. Y., Kacmarek, C. N. & Schleider, J. L. Economic Evaluations of Mental Health Programs for Children and Adolescents in the United States: A Systematic Review. *Clin. Child Fam. Psychol. Rev.* **24**, 1–19 (2021).
166. Van Ballegooijen, W. *et al.* Adherence to Internet-based and face-to-face cognitive behavioural therapy for depression: a meta-analysis. *PLoS One* **9**, e100674 (2014).
167. Furukawa, T. A. *et al.* Waiting list may be a nocebo condition in psychotherapy trials: a contribution from network meta-analysis. *Acta Psychiatr. Scand.* **130**, 181–192 (2014).
168. Mohr, D. C. *et al.* Control condition design and implementation features in controlled trials: a meta-analysis of trials evaluating psychotherapy for depression. *Transl. Behav. Med.* **4**, 407–423 (2014).
169. Sacristán, J. A., Abellán-Perpiñán, J. M., Dilla, T., Soto, J. & Oliva, J. Some reflections on the use of inappropriate comparators in CEA. *Cost Eff. Resour. Alloc.* **18**, 1–6 (2020).
170. Cox, B. J., Swinson, R. P., Direnfeld, D. M. & Bourdeau, D. Social desirability and self-reports of alcohol abuse in anxiety disorder patients. *Behav. Res. Ther.* **32**, 175–178 (1994).
171. Coughlin, S. S. Recall bias in epidemiologic studies. *J. Clin. Epidemiol.* **43**, 87–91 (1990).
172. Lensberg, B. R. *et al.* Challenges in measuring and valuing productivity costs, and their relevance in mood disorders. *Clin. Outcomes Res.* **5**, 565–573 (2013).
173. Johns, G. & Miraglia, M. The reliability, validity, and accuracy of self-reported absenteeism from work: A meta-analysis. *J. Occup. Health Psychol.* **20**, 1–14 (2015).
174. Beatty, L. & Binnion, C. A Systematic Review of Predictors of, and Reasons for, Adherence to Online Psychological Interventions. *Int. J. Behav. Med.* **23**, 776–794 (2016).
175. Karyotaki, E. *et al.* Predictors of treatment dropout in self-guided web-based interventions for depression: an 'individual patient data' meta-analysis. *Psychol. Med.* **45**, 2717–2726 (2015).
176. Briggs, A. Economic evaluation and clinical trials: size matters. *BMJ* **321**, 1362–3 (2000).
177. Briggs, A. H. & Gray, A. Handling uncertainty when performing economic evaluation of healthcare interventions. *Heal. Techn Assess* **3**, (1999).

178. Kolovos, S. *et al.* Cost effectiveness of guided Internet-based interventions for depression in comparison with control conditions: An individual–participant data meta-analysis. *Depress. Anxiety* **35**, 209–219 (2018).
179. Ebert, D. D. & Baumeister, H. Internet-Based Self-help Interventions for Depression in Routine Care. *JAMA Psychiatry* **74**, 852 (2017).
180. Abraham, M. B. *et al.* The Importance of the Hawthorne Effect on Psychological Outcomes Unveiled in a Randomized Controlled Trial of Diabetes Technology. *J. Diabetes Sci. Technol.* **12**, 735–736 (2018).
181. Dams, J. *et al.* Excess costs of social anxiety disorder in Germany. *J. Affect. Disord.* **213**, 23–29 (2017).
182. Bandelow, B. *et al. S3-Leitlinie Behandlung von Angststörungen: Version 2*. (AWMF, 2021).
183. Kählke, F. *et al.* Efficacy of an unguided internet-based self-help intervention for social anxiety disorder in university students: A randomized controlled trial. *Int. J. Methods Psychiatr. Res.* **28**, e1766 (2019).
184. Ebert, D. D. *et al.* Barriers of mental health treatment utilization among first year college students: First cross-national results from the WHO World Mental Health International College Student Initiative. *Int. J. Methods Psychiatr. Res.* **28**, e1782 (2019).
185. Esfandiari, N., Mazaheri, M. A., Akbari-Zardkhaneh, S., Sadeghi-Firoozabadi, V. & Cheraghi, M. Internet-Delivered Versus Face-to-Face Cognitive Behavior Therapy for Anxiety Disorders: Systematic Review and Meta-Analysis. *Int. J. Prev. Med.* **12**, (2021).
186. Jones, E. A. K., Mitra, A. K. & Bhuiyan, A. R. Impact of covid-19 on mental health in adolescents: A systematic review. *Int. J. Environ. Res. Public Health* **18**, 1–9 (2021).
187. Gomes, M., Murray, E. & Raftery, J. Economic Evaluation of Digital Health Interventions: Methodological Issues and Recommendations for Practice. *Pharmacoeconomics* **40**, 367–378 (2022).
188. Zarski, A.-C. *et al.* Adherence to Internet-Based Mobile-Supported Stress Management: A Pooled Analysis of Individual Participant Data From Three Randomized Controlled Trials. *J. Med. Internet Res.* **18**, e146 (2016).
189. Weeks, J. W. & Howell, A. N. The Bivalent Fear of Evaluation Model of Social Anxiety: Further Integrating Findings on Fears of Positive and Negative Evaluation. *Cogn. Behav. Ther.* **41**, 83–95 (2012).
190. Berger, T. *et al.* Behaviour Research and Therapy Internet-based treatment of social phobia : A randomized controlled trial comparing unguided with two types of guided

self-help. *Behav. Res. Ther.* **49**, 158–169 (2011).

191. Meyer, B., Alexander, Z. & Dilba, D. *Entspann dich, Deutschland! TK-Stressstudie 2021*. https://www.tk.de/resource/blob/2116464/9ff316aaf08870ed54aa8a664502ac67/2021-stressstudie-data.pdf (2021).
192. Schmidt, B. *et al.* A Comparison of Job Stress Models: Associations With Employee Well-Being, Absenteeism, Presenteeism, and Resulting Costs. *J. Occup. Environ. Med.* **61**, 535–544 (2019).
193. Rose, G. Sick individuals and sick populations. *Int. J. Epidemiol.* **30**, 427–432 (2001).
194. Nixon, P., Boß, L., Heber, E., Ebert, D. D. & Lehr, D. A three-armed randomised controlled trial investigating the comparative impact of guidance on the efficacy of a web-based stress management intervention and health impairing and promoting mechanisms of prevention. *BMC Public Health* **21**, 1–18 (2021).
195. Harrer, M. *et al.* Effect of an internet- and app-based stress intervention compared to online psychoeducation in university students with depressive symptoms: Results of a randomized controlled trial. *Internet Interv.* **24**, 100374 (2021).
196. Ebert, D. D. *et al.* Effectiveness and Moderators of an Internet-Based Mobile-Supported Stress Management Intervention as a Universal Prevention Approach: Randomized Controlled Trial. *J. Med. Internet Res.* **23**, e22107 (2021).
197. Ebert, D. D. *et al.* Internet- and mobile-based stress management for employees with adherence-focused guidance: efficacy and mechanism of change. *Scand J Work Env. Heal.* **42**, 382–394 (2016).
198. Ebert, D. D. *et al.* Self-guided internet-based and mobile-based stress management for employees: results of a randomised controlled trial. *Occup. Environ. Med.* **73**, 315–323 (2016).
199. Gerlinger, G., Mangiapane, N. & Sander, J. Digital health applications (DiGA) in medical and psychotherapeutic care. Opportunities and challenges from the perspective of the healthcare providers. *Bundesgesundheitsblatt - Gesundheitsforsch. - Gesundheitsschutz* **64**, 1213–1219 (2021).
200. Bundesinstitut für Arzneimittel und Medizinprodukte. DiGA Verzeichnis. *HelloBetter Stress and Burnout* https://diga.bfarm.de/de/verzeichnis/965 (2022).
201. GKV Spitzenverband. *Leitfaden Prävention Handlungsfelder und Kriterien nach § 20 SGB V*. (Georg Thieme Verlag KG, 2021). doi:10.1055/a-0739-9933.
202. Littlewood, E. *et al.* A randomised controlled trial of computerised cognitive behaviour therapy for the treatment of depression in primary care: the Randomised Evaluation of

the Effectiveness and Acceptability of Computerised Therapy (REEACT) trial. *Health Technol. Assess.* **19**, (2015).

203. Brabyn, S. *et al.* The second Randomised Evaluation of the Effectiveness, cost-effectiveness and Acceptability of Computerised Therapy (REEACT-2) trial: does the provision of telephone support enhance the effectiveness of computer-delivered cognitive behaviour therapy? A ra. *Health Technol. Assess.* **20**, 1–64 (2016).
204. Singal, A. G., Higgins, P. D. R. & Waljee, A. K. A primer on effectiveness and efficacy trials. *Clin. Transl. Gastroenterol.* **5**, e45 (2014).
205. Etzelmueller, A. *et al.* Effects of internet-based cognitive behavioral therapy in routine care for adults in treatment for depression and anxiety: Systematic review and meta-analysis. *J. Med. Internet Res.* **22**, e18100 (2020).
206. Vis, C. *et al.* Improving implementation of emental health for mood disorders in routine practice: Systematic review of barriers and facilitating factors. *JMIR Ment. Heal.* **5**, e9769 (2018).
207. Freund, J. *et al.* Digital prevention of depression for farmers? A qualitative study on participants' experiences regarding determinants of acceptance and satisfaction with a tailored guided internet intervention program. *Internet Interv.* **29**, 100566 (2022).
208. Titzler, I., Saruhanjan, K., Berking, M., Riper, H. & Ebert, D. D. Barriers and facilitators for the implementation of blended psychotherapy for depression: A qualitative pilot study of therapists' perspective. *Internet Interv.* **12**, 150–164 (2018).
209. Fuhr, K. *et al.* The association between adherence and outcome in an Internet intervention for depression. *J. Affect. Disord.* **229**, 443–449 (2018).
210. Ryan, C., Bergin, M. & Wells, J. S. Theoretical Perspectives of Adherence to Web-Based Interventions: a Scoping Review. *Int. J. Behav. Med.* **25**, 17–29 (2018).
211. Oinas-Kukkonen, H. & Harjumaa, M. Persuasive Systems Design. in *Routledge Handbook of Policy Design* 87–105 (Routledge, 2021). doi:10.4324/9781351252928-6.
212. McCall, H. C., Hadjistavropoulos, H. D. & Sundström, C. R. F. Exploring the role of persuasive design in unguided internet-delivered cognitive behavioral therapy for depression and anxiety among adults: Systematic review, meta-analysis, and meta-regression. *J. Med. Internet Res.* **23**, e26939 (2021).
213. Deterding, S., Dixon, D., Khaled, R. & Nacke, L. From game design elements to gamefulness: Defining 'gamification'. in *Proceedings of the 15th International Academic MindTrek Conference: Envisioning Future Media Environments, MindTrek 2011* 9–15 (2011). doi:10.1145/2181037.2181040.

214. Floryan, M., Chow, P. I., Schueller, S. M. & Ritterband, L. M. The Model of Gamification Principles for Digital Health Interventions: Evaluation of Validity and Potential Utility. *J. Med. Internet Res.* **22**, e16506 (2020).
215. Costache, M. E. *et al.* Higher- and lower-order personality traits and cluster subtypes in social anxiety disorder. *PLoS One* **15**, e0232187 (2020).
216. Moukheiber, A. *et al.* Gaze avoidance in social phobia: objective measure and correlates. *Behav. Res. Ther.* **48**, 147–151 (2010).
217. Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen. IQWiG's tasks and objectives [Aufgaben und Ziele der IQWiG]. https://www.iqwig.de/ueber-uns/aufgaben-und-ziele/ (2022).
218. Husereau, D. *et al.* Consolidated Health Economic Evaluation Reporting Standards (CHEERS) statement. *Eur. J. Heal. Econ.* **14**, 367–372 (2013).
219. Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen. *IQWiG Allgemeine Methoden. Version 6.1 vom 24.01.2022*. (2022).
220. Rogowski, W. H. Evaluation as institution: a contractarian argument for needs-based economic evaluation. *BMC Med. Ethics* **19**, 1–11 (2018).
221. Caro, J. J. *et al.* The efficiency frontier approach to economic evaluation of health-care interventions. *Health Econ.* **19**, 1117–1127 (2010).
222. Gandjour, A. Willingness to pay for new medicines: A step towards narrowing the gap between NICE and IQWiG. *BMC Health Serv. Res.* **20**, 1–7 (2020).
223. Gerber-Grote, A. *et al.* Decision making in Germany: Is health economic evaluation as a supporting tool a sleeping beauty? *Z. Evid. Fortbild. Qual. Gesundhwes.* **108**, 390–396 (2014).
224. *Proposal for a regulation of the European Parliament and of the Council on health technology assessment and amending Directive 2011/24/EU.* (European Commission, 2018).
225. Geinitz, C. Krankenkassen schreiben wegen Corona höchstes Defizit seit 2003. *Frankfurter Allgemeine Zeitung* https://www.faz.net/aktuell/wirtschaft/krankenkassen-schreiben-wegen-corona-hoechstes-defizit-seit-2003-17205639.html (2021).
226. Gensorowsky, D., Witte, J., Batram, M. & Greiner, W. Market access and value-based pricing of digital health applications in Germany. *Cost Eff. Resour. Alloc.* **20**, (2022).
227. Ramsey, S. D. *et al.* Cost-Effectiveness Analysis Alongside Clinical Trials II—An ISPOR Good Research Practices Task Force Report. *Value Heal.* **18**, 161–172 (2015).
228. Thielen, F. W. *et al.* How to prepare a systematic review of economic evaluations for

clinical practice guidelines: database selection and search strategy development (part 2/3). *Expert Rev. Pharmacoecon. Outcomes Res.* **16**, 705–721 (2016).

229. Mojtabai, R. *et al.* Barriers to mental health treatment: Results from the National Comorbidity Survey Replication. *Psychol. Med.* **41**, 1751–1761 (2011).

6. Appendix

List of Publications

Peer-reviewed

Ebert, D.D., **Kählke F.**, Buntrock, C., Berking, M., Smit, F., Heber, E., Baumeister, H., Funk, B., Riper, H., Lehr, D. A Health Economic Outcome Evaluation of an Internet-Based Mobile-Supported Stress Management Intervention for Employees. *Scandinavian Journal of Work, Environment & Health* **44**, 171-182 (2018). https://doi.org/10.5271/sjweh.3691

Kählke, F. & Ebert, D. D. Gesundheitsökonomische Evaluation von internet- und mobilbasierten Interventionen (IMI) zur Behandlung von psychischen Störungen: Ein Überblick. in *Gesundheit und Arbeit 4.0. Wenn Digitalisierung auf Mitarbeitergesundheit trifft.* (eds. Matusiewicz, D., Nürnberg, V. & Nobis, S.) 279–296 (Medhochzwei Verlag, 2018).

Ebert, D.D., Van Daele, T., Nordgreen, T., Karekla, M., Compare, A., Zarbo, C., Brugnera, A., Øverland, S., Trebbi, G., Jensen, K. L., **Kählke, F.** & Baumeister, H. (2018). Internet-and mobile-based psychological interventions: applications, efficacy, and potential for improving mental health. A report of the EFPA E-Health Taskforce *Eur. Psychol.* **23**, 167–187 (2018). https://doi.org/10.1027/1016-9040/a000318

Apolinário-Hagen, J., Harrer, M., **Kählke, F**., Fritsche, L., Salewski, C., & Ebert, D. D. Public attitudes toward guided internet-based therapies: Web-based survey study. *J. Med. Internet Res.* **20**, (2018). https://doi.org/10.2196/10735

Kählke, F., Berger, T., Schulz, A., Baumeister, H., Berking, M., Cuijpers, P., Bruffaerts, R., Auerbach, R.P., Kessler, R.C., Ebert D.D. Efficacy and Cost-effectiveness of an Unguided, Internet-and Mobile-based Self-Help Intervention for Social Anxiety Disorder in University Students: Protocol of a Randomized Controlled Trial. *BMC Psychiatry* **19**, 197 (2019). https://doi.org/10.1186/s12888-019-2125-4

Kählke, F., Berger, T., Schulz, A., Baumeister, H., Berking, M., Auerbach, R.P., Bruffaerts, R., Cuijpers, P., Kessler, R.C., Ebert D.D. Efficacy of an Unguided Internet-Based Self-Help Intervention for Social Anxiety Disorder in University Students: A Randomized Controlled Trial. *International Journal of Methods in Psychiatric Research* **28**, e1766 (2019). https://doi.org/10.1002/mpr.1766

Kählke, F., Buntrock, C., Smit, F., Berking, M., Lehr, D., Heber, E., Funk, B., Riper, H., Ebert, D.D. Economic Evaluation of an Internet-Based Stress-Management Intervention Alongside a Randomized Controlled Trial *Journal of Medical Internet Research Mental Health* **6**, e10866 (2019). https://doi.org/10.2196/10866

Kählke, F., Küchler, A.-M., Baumeister, H. & Ebert, D. D. StudiCare erfolgreich und gesund studieren-ein umfassendes deutsches und internationales Projekt zur Förderung der psychischen Gesundheit von Studierenden. *Fachzeitschrift für Onlineberatung und Comput. Kommun.* **15**, 133–156 (2019). https://www.e-beratungsjournal.net/wp-content/uploads/2019/07/kaehlke_et_al.pdf

Ebert, D. D., Franke, M., **Kählke, F.,** Kuechler, A.-M., Bruffaerts, R., Mortier, P., Karyotaki, E., Alonso, J., Cuijpers, P., Berking, M., Auerbach, R. P., Kessler, R. C. & Baumeister, H. On behalf of the WHO World Mental Health – International College Student collaborators Increasing intentions to use mental health services among university students. Results of a pilot randomized controlled trial within the World Health Organization's World Mental Health International College Student Initiative. *Int. J. Methods Psychiatr. Res.* **28**, e1754 (2019). https://doi.org/10.1002/mpr.1754

Paganini, S., Lin, J., **Kählke, F.,** Buntrock, C., Leiding, D., Ebert, D. D., & Baumeister, H. A guided and unguided internet- and mobile-based intervention for chronic pain: Health economic evaluation alongside a randomised controlled trial. *BMJ Open* **9**, (2019). https://doi.org/10.1136/bmjopen-2018-023390

Ebert D. D., Mortier P., **Kaehlke, F.,** Bruffaerts, R., Baumeister, H., Auerbach, R. P., Alonso, J., Vilagut, G., Martínez., K. U., Lochner, C., Cuijpers, P., Kuechler, A.-M., Green, J., Hasking, P., Lapsley, C., Sampson, N. A. & Kessler, R. C. On behalf of the WHO World Mental Health-International College Student Initiative collaborators. Barriers of mental health

treatment utilization among first year college students: First cross-national results from the WHO World Mental Health International College Student Initiative. *Int. J. Methods Psychiatr. Res.* **28**, e1782 (2019). https://doi.org/10.1002/mpr.1782

Buntrock, C., **Kählke, F.,** Smit, F. & Ebert, D. D. A systematic review of trial-based economic evaluations of internet- and mobile-based interventions for substance use disorders. *Eur. J. Public Health* **31**, i19–i28 (2021). https://doi.org/10.1093/eurpub/ckz022

Küchler, A. M., **Kählke, F**., Vollbrecht, D., Peip, K., Ebert, D.D. & Baumeister, H. Effectiveness, Acceptability, and Mechanisms of Change of the Internet-Based Intervention StudiCare Mindfulness for College Students: a Randomized Controlled Trial. *Mindfulness.* **13**, 2140–2154 (2022). https://doi.org/10.1007/s12671-022-01949-w

In press

Kählke, F., Buntrock, C., Smit, F., Ebert, D.D. Systematic review of economic evaluations for Internet- and mobile-based interventions for mental health problems *Nature Digital Medicine,* **Accepted** (2022)

Under review

Kählke, F., Buntrock, C., Smit, F., Berger, T., Baumeister, H., Ebert, D.D. Long-term Outcomes and Cost-effectiveness of an Internet- and Mobile-based Self-help Intervention for Social Anxiety Disorder in University Students: A Randomized Controlled Trial. *Nature Human Behavior,* **Submitted** (2022).

About the Author

Fanny Kählke was born in 1988, in Lauchhammer, Germany. She first graduated in Vocational Education with a major in Nursing and Health and a second major in Economics and Social studies from the Technische Universität Dresden in 2013, having acquired practical experience in a nursing home for the impaired and elderly. In 2014, she then graduated with distinction from Umeå Universitet, Sweden, in an international Master of Science program for Public Health. She subsequently qualified as a vocational teacher during her traineeship (Referendariat) at the vocational college for "Health and Social Care" Johanna Just in Potsdam. Afterwards, she kicked off her PhD studies at the Friedrich-Alexander-Universität Erlangen-Nürnberg in the Department of Clinical Psychology and Psychotherapy in 2016 under David Ebert, focusing on the StudiCare project for the prevention and health promotion of mental health in students, which is part of the World Mental Health International College Student (WMH-ICS) initiative. After a parental leave from 2019 to 2021, she concluded her dissertation at David Ebert's Professorship for Psychology and Digital Mental Health at the Technische Universität München, now also focusing on teaching students on topics related to psychological prevention.