Economic evaluation of an internet-based stress-management intervention alongside an RCT

Fanny Kählke M. Ed. MPH\textsuperscript{1}, Claudia Buntrock\textsuperscript{1} MSC, Filip Smit\textsuperscript{2,3,4} PhD, Matthias Berking\textsuperscript{1} PhD, Dirk Lehr\textsuperscript{5} PhD, Elena Heber\textsuperscript{6} PhD, Burkhardt Funk\textsuperscript{5} PhD, Heleen Riper\textsuperscript{2,7} PhD, David Daniel Ebert\textsuperscript{1} PhD

\textsuperscript{1} Department of Clinical Psychology and Psychotherapy, University of Erlangen- Nuremberg, Erlangen, Germany
\textsuperscript{2} Department of Clinical, Neuro and Developmental Psychology, Amsterdam Public Health research institute, Vrije Universiteit, Amsterdam, Netherlands
\textsuperscript{3} Department of Epidemiology and Biostatistics, Amsterdam Public Health research institute, VU University Medical Centre, Amsterdam, Netherlands
\textsuperscript{4} Centre of Health-Economic Evaluation, Trimbos Institute (Netherlands Institute of Public Mental Health), Utrecht, Netherlands
\textsuperscript{5} Department of Health Psychology and Applied Biological Psychology, Leuphana University, Lueneburg
\textsuperscript{6} GET.ON Institute for Online Health Trainings, Hamburg, Germany
\textsuperscript{7} Telepsychiatric Centre, University of Southern Denmark, Odense, Denmark

*Corresponding author

Fanny Kählke, M. Ed. MPH\textsuperscript{1}

Friedrich-Alexander University Erlangen-Nuremberg
Department of Clinical Psychology and Psychotherapy
Nägelsbachstrasse 25a
Erlangen, 91052
Germany
Phone: 49 9131 85 - 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 the society. Internet-based stress management interventions (iSMI) are effective in reducing such stress. However, evidence for their cost-effectiveness is scant.

Objective:
The aim of the study was to conduct a cost-effectiveness (CEA) and a cost-utility (CUA) analysis of a guided iSMI for employees.

Methods:
A sample of 264 employees with elevated symptoms of perceived stress (Perceived Stress Scale, PSS-10 ≥ 22) was assigned to the iSMI or a waitlist control condition (WLC) with unrestricted access to treatment as usual. Participants were recruited in Germany in 2013, followed through 2014, and data analyzed in 2017. The iSMI consisted of 7 sessions plus one booster session and was based on problem-solving and emotion regulation techniques. Costs were measured from the societal perspective, including all direct and indirect medical. Costs were related to symptomatic remission in the CEA and to gains in quality adjusted life years (QALYs) in the CUA. Statistical uncertainty was handled using bootstrapping (N=5000).

Results:
At a willingness-to-pay (WTP) ceiling of €0 for becoming free of self-perceived stress symptoms, there was a 70% probability of the intervention being more cost-effective than WLC. This rose to 85% and 93% when society is willing to pay €1000 and €2000 achieving symptomatic remission. The CUA yielded a 76% probability of the intervention being more cost-effective than WLC at a conservative WTP threshold of €20,000 ($25,800) per QALY gained.

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

Trial Registration:
German Clinical Trials Register (DRKS): 00004749; http://drks-neu.uniklinik-freiburg.de/drks_web/setLocale_EN.do (Archived by WebCite at http://www.webcitation.org/6e8rl98nl )
Introduction

Up to 20% of the workforce in Europe suffers from elevated stress levels [1]. Prolonged stress levels are associated with deteriorations in psychological and physiological health. Therefore, there is a demand for health care interventions that can be implemented at scale for affordable costs. Web-based and mobile-based interventions meet these requirements. In a recent meta-analysis, internet-based stress management interventions (iSMIs) have been found to be effective with a pooled effect size of $d=0.43$ (CI: 0.31-0.54) on perceived stress [2]. It is often argued that internet-based interventions can be cost-effective, but little evidence exists. To the best of our knowledge economic evaluations concerning iSMIs are not available. Hedman et al. (2016) compared a behavioral stress management program to an ICBT for treatment of health anxiety, where the iSMI resulted in lower costs [3]. The present study aimed to investigate the cost-effectiveness and cost-utility of an iSMI versus a 6-month waitlist control group with unrestricted access to treatment as usual (TAU).

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 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 to a waitlist control condition (WTC) with access to TAU [4]. The present health-economic evaluation followed 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) [5, 6]. 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 a web-based randomization program (Randlist) [4]. 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 standard deviation (SD 6.2) above the mean (PSS-10=15.3) in a large working population [7] 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 being diagnosed with a psy-
chosis. 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 GET.ON Stress intervention consisted of seven sessions. A booster session is offered four weeks after training completion. The iSMI was based on Lazarus’s transactional model of stress [8]. It employs both problem solving [9, 10] and emotion regulation strategies [11] as well as principles of health behavior change. A detailed description of the iSMI can be found elsewhere.[12] The clinical effectiveness of the iSMI has been positively evaluated in a series of RCT’s [4, 13-16].

**Outcome measures**

Self-reported measures of stress and social functioning (PSS-10 and 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 [17]. Cronbach’s alphas indicated that the internal consistency ranged from .70 to .91 over different measurement points in this study [15]. Symptom-free status was operationalized as scoring 2 SDs below the PSS-10 sample mean at T1 (mean 25.52, SD 3.91) [4, 18].

**Quality-Adjusted Life Years (QALYs)**

QALYs were used as the primary outcome in the cost-utility analysis. QALYs were computed using the SF-6D [19]. 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 [20].

**Resource Use and Costing**

We assessed direct and indirect costs, which occurred three month prior to the assessment, at baseline and 6-month follow-up. All costs were calculated in Euros (€) for the reference year 2013 (index factor 1.04 based on year 2010) referring to the German consumer price index [21]. 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 $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 [22]. The TiC-P 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 [23-29]. The German version has been used in a number of health economic evaluations alongside randomized trials [24, 25, 27, 29, 30]. The standard unit cost prices were multiplied by the units of resource use for each participant. Table 1 presents direct medical and direct non-medical costs by health service type. Cumulated costs of the trial were estimated using the area under curve (AUC) method to linearly interpolate three months costs as measured at each measurement point to cover the full follow-up period of six months [31].

Health Care Costs

Health care costs were calculated according to the guidelines of Kraut and Bock et al. [32, 33]. We included unit costs for a physician, medical specialist and psychological services such as psychiatrist and psychotherapist, and paramedical services such as physiotherapy, massage, ergotherapy as well as inpatient care and rehabilitation.

Medication

Unit costs of prescription drugs were calculated using the German register for pharmaceutical drugs “Rote Liste”. [34] Our calculation was conducted in three steps: (1) computation of the mean manufacture’s retail price of the 3 largest packages with the same agent (based on the reported daily dose), (2) deduction of the pharmacist’s claw back, and (3) weighting by the statutory population share (89% 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 ($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, used the iSMI in their leisure time after working hours. Hence, these costs were not included.

Patient and Family Costs

Self-reported out-of-pocket expenses as well as the direct non-medical costs due to the distance travelled to make a return trip to a health-care service were collected. Accordingly, participants were asked to report the cost of travelling by bus or taxi; each kilometer by car was valued at €0.30. [35] Additionally, opportunity costs defined as the benefit that is given up to
acquire something else, e.g. time spent on the intervention, waiting times for and receiving treatment by a physician, were valued at €23.10 per hour [32]. The costs of informal care from family and friends was put at €18.33 per hour, which is a shadow price corresponding with the hourly payment for a housekeeper [32].

**Costs of Productivity Losses**

Absenteeism costs were calculated by applying the human capital approach [36]. 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 work-days for which they reported lesser efficiency. Based on the Osterhaus method [37], 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. Productivity losses caused by unpaid work such as daily chores were valued using a shadow price of €18.33 per hour for domestic help.

**Table 1.** Unit costs for the type of health service utilized by the participants.

<table>
<thead>
<tr>
<th>Health service type</th>
<th>Unit</th>
<th>Costs (€)¹</th>
</tr>
</thead>
<tbody>
<tr>
<td>Physician</td>
<td></td>
<td>20.57</td>
</tr>
<tr>
<td>Gynecologist</td>
<td></td>
<td>31.27</td>
</tr>
<tr>
<td>Orthopedist</td>
<td></td>
<td>25.53</td>
</tr>
<tr>
<td>Specialists for internal medicine</td>
<td></td>
<td>63.53</td>
</tr>
<tr>
<td>Ophthalmologist</td>
<td></td>
<td>36.55</td>
</tr>
<tr>
<td>Dermatologist</td>
<td></td>
<td>19.36</td>
</tr>
<tr>
<td>ETN specialist</td>
<td></td>
<td>27.80</td>
</tr>
<tr>
<td>Surgeon</td>
<td></td>
<td>44.09</td>
</tr>
<tr>
<td>Urologist</td>
<td></td>
<td>25.20</td>
</tr>
<tr>
<td>Neurologist</td>
<td></td>
<td>46.49</td>
</tr>
<tr>
<td>Psychotherapist</td>
<td></td>
<td>78.53</td>
</tr>
<tr>
<td>Dentist</td>
<td></td>
<td>54.62</td>
</tr>
<tr>
<td>Logopedics / speech therapy</td>
<td>Contact</td>
<td>40.56</td>
</tr>
<tr>
<td>Physiotherapy</td>
<td></td>
<td>17.30</td>
</tr>
<tr>
<td>Ergotherapy / occupational therapy</td>
<td></td>
<td>39.01</td>
</tr>
<tr>
<td>Mean remedies</td>
<td></td>
<td>32.29</td>
</tr>
</tbody>
</table>
### 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 is 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 [38]. This procedure takes the stochastic uncertainty of the trial data into account[39] 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 was imputed using the regression imputation procedure implemented in Stata to obtain 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-squared test. At baseline, mean SF-6D utility values were similar in both groups (WLC=0.65 SD=0.08 and iSMI=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

#### Cost-effectiveness analyses

For the cost-effectiveness analyses, the incremental cost-effectiveness ratio (ICER) was calculated as incremental costs per unit of effect (QALY, symptom-free status). The incremental

<table>
<thead>
<tr>
<th>Service Type</th>
<th>Unit Costs</th>
</tr>
</thead>
<tbody>
<tr>
<td>General hospital / inpatient</td>
<td>648.11</td>
</tr>
<tr>
<td>Mental hospital / inpatient</td>
<td>348.26</td>
</tr>
<tr>
<td>General hospital / day patient</td>
<td>421.27</td>
</tr>
<tr>
<td>Mental hospital / day patient</td>
<td>226.37</td>
</tr>
<tr>
<td>Rehabilitation / outpatient</td>
<td>49.43</td>
</tr>
<tr>
<td>Rehabilitation / day patient</td>
<td>93.81</td>
</tr>
<tr>
<td>Rehabilitation / inpatient</td>
<td>138.19</td>
</tr>
</tbody>
</table>

*Note: Unit costs were calculated for the year 2013[32] or adjusted by the German consumer price index for 2013.*
The cost-effectiveness ratio (ICER) was calculated as $\text{ICER} = \frac{(\text{costs}_{\text{SMI}} - \text{costs}_{\text{WLC}})(\text{effects}_{\text{SMI}} - \text{effects}_{\text{WLC}})}{\text{effects}_{\text{SMI}} - \text{effects}_{\text{WLC}}}$, 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 non-parametric 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 SURE model (seemingly unrelated regression equations) and allowed for correlated residuals of the cost and effect equations [40]. The 5000 bootstrap replications of costs and effects were also used to obtain 95% confidence intervals (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 one bootstrapped ICER.

Since the willingness-to-pay (WTP) ceiling for gaining one unit of health (e.g. gaining one QALY or obtaining symptomatic remission in one person) is an unknown quantity, a cost-effectiveness acceptability curve (CEAC) was presented, which displays the probability of the intervention being cost-effective for one additional unit of health gained at varying WTP ceilings. All analyses were performed using Stata version 13 [41].

**Sensitivity analyses**

The robustness of the outcomes was assessed using several sensitivity analyses. First, we used the EQ-5D-3L [42] 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 were only reported by few participants (n=9, 3.4%). Such outliers may lead to distorted outcomes results, so they were removed in a final sensitivity analysis.

**Results**

**Sample**

Table 2 presents baseline characteristics. The sample predominately consisted of fully employed middle-aged women living with a partner. A comprehensive description of the study sample and the participant flow can be found elsewhere [4]. We did not observe any clinical relevant baseline differences between study conditions.
Table 2. Demographic characteristics: means/counts, standard deviations/percentages at baseline

<table>
<thead>
<tr>
<th></th>
<th>All (n=264)</th>
<th>iSMI (n=132)</th>
<th>WLC (n=132)</th>
</tr>
</thead>
<tbody>
<tr>
<td>N (%)</td>
<td>M (SD)</td>
<td>N (%)</td>
<td>M (SD)</td>
</tr>
<tr>
<td>Sociodemographic</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>-</td>
<td>43.3 (10.2)</td>
<td>-</td>
</tr>
<tr>
<td>Gender, female, n (%)</td>
<td>193 (73.1)</td>
<td>-</td>
<td>97 (73.5)</td>
</tr>
<tr>
<td>Married/Partnership</td>
<td>160 (60.6)</td>
<td>-</td>
<td>80 (60.6)</td>
</tr>
<tr>
<td>Experience</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Experience with health</td>
<td>34 (12.9)</td>
<td>-</td>
<td>17 (12.9)</td>
</tr>
<tr>
<td>trainings</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Previous psychotherapy</td>
<td>95 (36.0)</td>
<td>-</td>
<td>52 (39.4)</td>
</tr>
<tr>
<td>Current psychotherapy</td>
<td>16 (6.1)</td>
<td>-</td>
<td>5 (3.8)</td>
</tr>
<tr>
<td>Work</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Characteristics</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Years of work experience</td>
<td>-</td>
<td>18.1 (11.1)</td>
<td>-</td>
</tr>
<tr>
<td>Full-time employed</td>
<td>204 (77.3)</td>
<td>-</td>
<td>105 (79.5)</td>
</tr>
<tr>
<td>Part-time employed</td>
<td>57 (21.6)</td>
<td>-</td>
<td>25 (18.9)</td>
</tr>
<tr>
<td>On sick leave</td>
<td>3 (1.1)</td>
<td>-</td>
<td>2 (1.5)</td>
</tr>
<tr>
<td>Work sectors</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Social</td>
<td>97 (36.7)</td>
<td>48 (36.4)</td>
<td>49 (37.1)</td>
</tr>
<tr>
<td>Service</td>
<td>43 (16.3)</td>
<td>21 (15.9)</td>
<td>22 (16.7)</td>
</tr>
<tr>
<td>Health</td>
<td>36 (13.6)</td>
<td>22 (16.7)</td>
<td>14 (10.6)</td>
</tr>
<tr>
<td>Economy</td>
<td>31 (11.7)</td>
<td>14 (10.6)</td>
<td>17 (12.9)</td>
</tr>
<tr>
<td>IT</td>
<td>15 (5.7)</td>
<td>8 (6.1)</td>
<td>7 (5.3)</td>
</tr>
<tr>
<td>Others</td>
<td>42 (16.0)</td>
<td>19 (14.3)</td>
<td>23 (17.4)</td>
</tr>
</tbody>
</table>

Study drop-outs

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 ($\chi^2=1.44; \text{df}=1; P=.23$).

Outcome measures

The iSMI improved by 9.75 (SD 6) PSS-10 stress scores between pre and 6-month follow up whereas the WLC improved by 3.0 scores (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%; $\chi^2=35.91; \text{df}=1; P<.001; \text{NNT}=2.75, 95\% \text{ CI 2.11-3.95}$) [4]. 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 ($4178) in the iSMI and €3183 ($4178) in the WLC, which is only a small difference of €56 ($72), indicating that randomization had resulted in a well-balanced trial. Table 3 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 ($490) in favor of the intervention group (iSMI: €5258, WLC: €5642). Health care costs were, on average, higher in the iSMI group compared to WLC. Hospital admissions were a major cost driver. Regarding the patient and family costs, the costs were in favor of the iSMI. Informal care were decreased by €241 for the iSMI. Finally, productivity losses produced the highest cost differences of €487 favoring the intervention and exceeding the intervention costs.

Table 3 Average costs per participant (in €) by condition at 6-months follow-up (Area under the curve, intention-to-treat-sample, n=264).

<table>
<thead>
<tr>
<th></th>
<th>iSMI (n=132)</th>
<th>WLC (n=132)</th>
<th>Incremental costs</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean (SD), €</td>
<td>Mean (SD), €</td>
<td>Difference, €</td>
</tr>
<tr>
<td><strong>Health care costs</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intervention</td>
<td>299 (139)</td>
<td>0 (175)</td>
<td>299</td>
</tr>
<tr>
<td>Physician services</td>
<td>132 (139)</td>
<td>147 (2222)</td>
<td>-15</td>
</tr>
<tr>
<td>Psychological services</td>
<td>111 (291)</td>
<td>209 (468)</td>
<td>-98</td>
</tr>
<tr>
<td>Hospital in-patient</td>
<td>342 (2222)</td>
<td>188 (1237)</td>
<td>154</td>
</tr>
<tr>
<td>Hospital semi-residential</td>
<td>234 (1444)</td>
<td>77 (798)</td>
<td>157</td>
</tr>
<tr>
<td>Rehabilitation</td>
<td>8 (41)</td>
<td>89 (658)</td>
<td>-81</td>
</tr>
<tr>
<td>Non-physician services</td>
<td>167 (293)</td>
<td>174 (314)</td>
<td>-7</td>
</tr>
<tr>
<td>Prescription drugs</td>
<td>50 (97)</td>
<td>56 (105)</td>
<td>-6</td>
</tr>
<tr>
<td><strong>Patient and family costs</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Over the counter drugs</td>
<td>48 (88)</td>
<td>48 (78)</td>
<td>0</td>
</tr>
<tr>
<td>Opportunity costs</td>
<td>485 (754)</td>
<td>526 (892)</td>
<td>-42</td>
</tr>
<tr>
<td>Travel expenses</td>
<td>27 (48)</td>
<td>49 (94)</td>
<td>-21</td>
</tr>
<tr>
<td>Domestic help /informal care</td>
<td>424 (1213)</td>
<td>665 (1327)</td>
<td>-241</td>
</tr>
<tr>
<td><strong>Productivity losses</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Absenteeism</td>
<td>1346 (2184)</td>
<td>1655 (3436)</td>
<td>-309</td>
</tr>
<tr>
<td>Presenteeism</td>
<td>1578 (1471)</td>
<td>1756 (1849)</td>
<td>-178</td>
</tr>
<tr>
<td><strong>Total costs</strong></td>
<td>5258 (5493)</td>
<td>5642 (6000)</td>
<td>-384</td>
</tr>
</tbody>
</table>

a Due to rounding, numbers presented may not add up precisely to the totals provide
Cost-effectiveness

Table 4 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 €1063. 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 health-economics 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%.

![Cost-effectiveness plane](image)

**Figure 1.** Scatterplot of 5000 replicates of the incremental cost-effectiveness ratio (mean differences in costs in symptom-free status) on the cost-effectiveness plane: iSMI intervention vs WLC.
Figure 2. Cost-effectiveness acceptability curve showing the probability of the Web-based guided self-help 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 (~0.001 QALYs gained) for lower mean costs (€-386; $-498). As seen in Figure 3, 69% of the simulated ICERs fell in the SE-Q reflecting the intervention’s probability of dominating WLC, while 26% fell in the NE-Q indicating higher costs and health gains, 2% fell in the SW-Q and 3% in NW-Q. Assuming a willingness-to-pay of €10,000, €20,000 for gaining one 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 [QALYs]) on the cost-effectiveness plane: iSMI intervention vs WLC.
Figure 4. Cost-effectiveness acceptability curve showing the probability of the Web-based guided self-help 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 [QALYs]).

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 to 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 a ceiling effects in milder conditions [20]. 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 few participants but were associated with high costs, hospital costs might have distorted the results. Excluding these costs led to higher ICERs for all outcome categories. 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.

Increasing, and subsequently reducing the intervention costs by €100, lead 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.

Table 4 Results of the main and sensitivity analysis based on 5000 bootstrap simulations.
<table>
<thead>
<tr>
<th></th>
<th>NE</th>
<th>SE</th>
<th>SW</th>
<th>NW</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Main analysis</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Perceived stress (range 0-40)</td>
<td>-386 (-1794 to 1006)</td>
<td>6.27 (4.9 to 7.7)*</td>
<td>-61 (-297 to 171)</td>
<td>30 70 - -</td>
</tr>
<tr>
<td>Symptom-free status (range: 0-1)</td>
<td>-386 (-1794 to 1006)</td>
<td>0.362 (0.25 to 0.47)*</td>
<td>-1063 (-5334 to 3360)</td>
<td>30 70 - -</td>
</tr>
<tr>
<td>QALYs (range: 0-1)</td>
<td>-386 (-1794 to 1006)</td>
<td>0.0074 (-0.015 to 0.016)</td>
<td>-49413*</td>
<td>26 69 2 3</td>
</tr>
<tr>
<td><strong>SA1</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Perceived stress (range 0-40)</td>
<td>-616 (-1731 to 485)</td>
<td>6.27 (4.9 to 7.7)*</td>
<td>-99 (-290 to 81)</td>
<td>13 87 - -</td>
</tr>
<tr>
<td>Symptom-free status (range: 0-1)</td>
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<td>-1737 (-5228 to 1415)</td>
<td>13 87 - -</td>
</tr>
<tr>
<td>QALYs (range: 0-1)</td>
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<td>0.0074 (-0.015 to 0.016)</td>
<td>-49671*</td>
<td>12 83 2 3</td>
</tr>
<tr>
<td><strong>SA2</strong></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Perceived stress (range 0-40)</td>
<td>-286 (-1694 to 1106)</td>
<td>6.27 (4.9 to 7.7)*</td>
<td>-45 (-281 to 187)</td>
<td>34 66 - -</td>
</tr>
<tr>
<td>Symptom-free status (range: 0-1)</td>
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<td>0.362 (0.25 to 0.47)*</td>
<td>-778 (-4985 to 3419)</td>
<td>34 66 - -</td>
</tr>
<tr>
<td>QALYs (range: 0-1)</td>
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<td>0.0075 (-0.015 to 0.016)</td>
<td>-31555*</td>
<td>31 64 2 3</td>
</tr>
<tr>
<td>Perceived stress (range 0-40)</td>
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<td>6.27 (4.9 to 7.7)*</td>
<td>-77 (-315 to 155)</td>
<td>24 76 - -</td>
</tr>
<tr>
<td>Symptom-free status (range: 0-1)</td>
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<td>0.362 (0.25 to 0.47)*</td>
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<tr>
<td>QALYs (range: 0-1)</td>
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<td>22 73 2 3</td>
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<tr>
<td><strong>SA3</strong></td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>QALYs (range: 0-1)</td>
<td>-386 (-1794 to 1006)</td>
<td>0.00186 (-0.010 to 0.014)</td>
<td>-191089*</td>
<td>49 14 22 16</td>
</tr>
</tbody>
</table>

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 of intervention costs, SA3 analyses for EQ5D QALY. Note costs are expressed in 2013 Euros.

*P < 0.05.

a 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.[43]

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 cost
Discussion

Main 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 to 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 to 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
Firstly, we had missing data, which was handled using imputation techniques to perform an ITT analysis of both effects and costs.[44] As drop out was very low (12.8% for the iSMI and 8.33% for the WTC at 6 months) it is unlikely that this has biased the results substantially. Secondly, the costs and effects were only evaluated over a 6 months period. Hence, we cannot draw any conclusions about long-term effects. Thirdly, self-reported costs and effect 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. Fourthly, 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. Finally, a waitlist control group design with unrestricted access to treatment as usual has been chosen which causes participants being less motivated to initiate health-related behavior changes, and thus over-accentuates effects [45].

Comparison with findings from other studies
The results of this study with an effect size of \( d=0.83 \) [4] on perceived stress are in line with the meta-analytic evidence (pooled effect size of \( d=0.43 \) (CI: 0.31-0.54)) [2].
Additionally, 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. (2002) evaluated the costs of a self- and professional-administered SMI not delivered online in patients undergoing chemotherapy compared to usual care [46]. Lower costs
and statistically higher quality of life outcomes were found in the intervention group. Hedman et al. (2016) compared a behavioral stress management to iCBT for treatment of severe health anxiety. The iSMI resulted in lower costs but was not considered cost-effective [47].

In a web-based intervention from Geraedts (2015) [48] the probabilities of cost-effectiveness were 0.62 (societal perspective) and 0.55 (employer’s perspective) compared to WLC in employees with depressive symptoms. The intervention was not judged cost-effective. Besides that, the reduction of depressive symptoms was rather small ($d=0.16$) [49] compared to our study ($d=0.64$) [4] at post measurement. However, Buntrock et al. (2017) 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 [30]. 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 study results 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 [50]. However, a meta-analytic evidence shows that guidance yield higher effect sizes [51]. 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.

**Conclusion**
This study demonstrated that the iSMI has a high probability of being cost-effective in reducing stress levels when compared to a wait-list control condition. Given the increasing stress in the workplace and the small number of people who are reached by available healthcare services [52], it would be worthwhile to integrate such iSMIs into routine occupational health care.

**Acknowledgements**

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**Declaration of Interest** DE, DL, EH and MB are stakeholders of the “Institute for Online Health Trainings”, that aims to transfer scientific knowledge related to the present research into routine health care.

**Abbreviations**

AUC: area under curve  
CEA: cost-effectiveness analysis  
CI: confidence intervals  
CUA: cost-utility analysis  
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  
SD: standard deviation  
TAU: treatment as usual  
TiC-P: Trimbos Institute and Institute of Medical Technology Questionnaire for Costs Associated with Psychiatric Illness  
WLC: waitlist control condition  
WTP: willingness-to-pay
References

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