# Chapter 5

# Effectiveness of a web-based guided self-help intervention in preventing the onset of major depression

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# Abstract

## Importance

Evidence-based treatments for Major Depressive Disorder (MDD) are not very successful in improving functional and health outcomes. Attention has increasingly been focused on the prevention of MDD.

## Objective

To evaluate the effectiveness of a web-based guided self-help intervention on the onset of MDD.

## Design, Setting and, Participants

Two-group randomized clinical trial conducted between March 1, 2013 and March 4, 2015. Participants were recruited in Germany from the general population via a large statutory health insurance company (i.e. insurance funded by joint employers-employees contributions). Participants included 406 self-selected adults with sub-threshold depression (Centre for Epidemiologic Studies Depression Scale ≥ 16, no current MDD according to DSM-IV-TR criteria).

## Intervention(s)

All participants had unrestricted access to care-as-usual (i.e. visits to the GP) and were randomized to either a web-based guided self-help intervention (i.e. cognitive-behavioral and problem-solving therapy supported by an online trainer; n = 202) or a web-based psycho-education (n = 204).

## Main Outcome and Measures

The primary outcome was time to onset of MDD in the intervention relative to the control group over a 12-month follow-up period as assessed by blind diagnostic raters using the telephone-administered structured clinical interview for DSM-IV Axis Disorders (SCID) at 6- and 12-month follow-up covering the period to the previous assessment.

## Results

Among 406 randomized patients (mean age 45, 73.9% women), 335 (82%) completed the telephone follow-up at 12 months. In the intervention group, 55 participants (34%) and 84 participants (49%) in the control group experienced an MDD. Cox regression analyses controlling for baseline depressive symptom severity showed a hazard ratio of 0.59 (95% CI 0.42 - 0.82; p = .002) at 12-month follow-up. The number needed to treat to avoid one new case of MDD was 5.9 (95% CI 3.9 - 14.6).

## Conclusions and Relevance

Among patients with sub-threshold depression, the use of a web-based guided self-help intervention compared to usual care reduced the incidence of MDD over 12 months. Further research is needed to understand whether the effects are generalizable to both first depression onset and depression recurrence as well as efficacy without the use of an online trainer.

# Introduction

Major depressive disorder (MDD) is a highly prevalent condition associated with a substantial disease burden and economic costs (1). The 12-month prevalence of MDD in high-income countries is estimated at 5.1% (2) with an annual incidence rate of 3% (3). MDD is projected to be the leading cause of premature mortality and disability in high-income countries by 2030 (4).

However, assuming the hypothetical scenario of 100% coverage and compliance to evidence-based treatments, approximately only one third of the disease burden attributable to MDD could be averted (5). Therefore, attention has increasingly been focused on the prevention of MDD. Recent meta-analytic evidence suggests that it is possible to prevent the onset of MDD using psychological interventions by targeting individuals with sub-threshold depression (i.e., indicated prevention) (6).

However, studies were heterogeneous and mostly directed at specific at-risk populations (i.e., pregnant women). Targeting at-risk groups becomes less relevant when offering low-cost interventions (i.e. web-based interventions). Advantages of web-based interventions include: (1) accessible at any time and place, (2) participants can work at their own pace and easily review materials, and (3) at-risk individuals are reached at an earlier stage as compared to traditional mental health services as web-based interventions are more easily integrated into daily life. Web-based interventions have been shown to be effective in reducing depressive symptoms (7) and to be acceptable to participants (8). To the best of our knowledge, no study has yet investigated the effectiveness of a web-based intervention on the onset of diagnosed MDD. This study evaluated the effect of a web based guided self-help intervention on the prevention of MDD onset in an adult population with sub-threshold depression. An earlier publication from this study reported interim outcomes at post-treatment and 6-month follow-up for depressive symptoms (9). In this study, we report the primary outcomes from this clinical trial, progression to MDD at 12 months.

# Methods

## Trial design and participants

The study protocol is available in chapter 3. In brief, a 2-group randomized clinical trial (RCT) was conducted to establish the effectiveness of a web-based guided self-help intervention compared to enhanced usual care on the onset of MDD. The study was approved by the medical ethics committee of the University of Marburg (reference number AZ 2012-35K) and registered in the German clinical trial registry. Participants provided written informed consent. Study

outcomes were assessed at baseline, post-treatment (secondary outcomes only), 6- and 12-month follow up.

German citizens are either privately (i.e. insurers charge a risk-related contribution; 11% of the German population) or statutorily insured (i.e. insurance funded by joint contributions based on a percentage of income by employers and employees to sickness funds; 89% of the population). Participants were mainly recruited via a large German statutory health insurance company (BARMER GEK) by announcing the study in its members' magazine. The BAMRER GEK reaches 12.2% (8.6 million) of the statutorily insured population in Germany. However, adults interested in participating in the study could apply for participation irrespectively of their insurance status. The study was also announced in newspaper articles, on-air media, and related websites. Individuals self-identifying as having a lower mood could apply online on the research website. Referral by a physician was not required. This open recruitment strategy was chosen to try to approximate the practice setting in which this type of web-based preventive intervention might be used.

Applicants were asked to complete an online screening questionnaire to assess whether they (a) experience sub-threshold depression (Center for Epidemiologic Studies Depression Scale (CES-D) ≥ 16) (10), (b) were aged 18 and above, (c) had Internet access, (d) were not currently receiving or (e) on a waiting list for psychotherapy, (f) had not received psychotherapy in the past six months, and (g) did not show a notable suicidal risk (Beck Depression Inventory item 9 > 1). The use of antidepressant medication was not an exclusion criterion as in Germany, antidepressants are commonly used for a wide range of indications (i.e. depression, anxiety disorders, obsessive-compulsory disorder, chronic pain syndrome, and stress urinary incontinence) (11). However, participants needed to be on a stable dose for at least four weeks to be able to enter the study. Potentially eligible participants were scheduled for a SCID interview to assess final eligibility: not meeting DSM-IV criteria for (a) a major depressive episode, (b) bipolar disorder, or (c) psychotic disorder, and (d) not having a history of a major depressive disorder in the past six months (based on Kupfer's model (12)). According to Kupfer's model, a patient is considered to be recovered when he or she stays in remission for a minimum of six months. In the baseline assessment, participants were asked to self-identify as either Caucasian, Black, or Hispanic.

## Randomization and masking

Randomization took place at an individual level and was conducted centrally by an independent researcher not otherwise involved in the study. For the randomization procedure an automated computer-generated random numbers table was used (randlist) that automatically assigned 0 (control group) or 1 (intervention group) to each participant's individual trial ID number. Trial

IDs were numbered sequentially and did not entail any specific information about participants (i.e., their initials). The randomization procedure was performed in order of incoming informed consent forms. The researcher who recruited participants (i.e. collecting informed consent forms) was not informed about participants' randomization status. Hence, this researcher could not influence the randomization procedure by re-ordering informed consent forms. The researcher conducting the randomization had no other information about the participant than his or her trial ID number. Block randomization of size two was used to ensure similar sample sizes across study groups. Study participants were aware of their allocation. SCID interviewers were, however, unaware of participants' randomization status. Steps taken to maintain blinding are described in detail elsewhere (9, 13). After each assessment, interviewers were asked to guess each participant's randomization status and these guesses were compared with the actual status. In case of evidence for blinding breakdown, the interviewer was changed to the second outcome interview. The research staff conducting SCID interviews were not otherwise involved in the study.

## Interventions

All study participants had unrestricted access to routine care. Care-as-usual for sub-threshold depression entails visits to the GP but no treatment provided by mental health care specialist. The German S3-Guideline/National Disease Management Guideline Unipolar Depression recommends psycho-education or more intensive psychological interventions and the prescription of antidepressant medication, if depressive symptoms deteriorate (i.e., diagnosed major depressive disorder) (14). In this pragmatic trial, care-as-usual was not protocolized. However, health care utilization was measured with the Trimbos/iMTA questionnaire for costs associated with psychiatric illness (15) so that a description of care-as-usual could be produced.

### Guided web-based intervention

The web-based intervention is a multimedia, interactive online tool consisting of six 30-minute sessions. However, the handling time of sessions could vary among users. Participants were advised to complete two sessions a week if possible but at least a minimum of one. The intervention is based on psycho-education, behavior therapy (BT) and problem-solving therapy (PST). The content of the intervention has been described in detail elsewhere (9, 13). During the training, participants were supported by an online trainer who provided written individual feedback after each session. Feedbacks focused on supporting participants to work through the exercises and no therapeutic advice was provided. Trained graduate students and health care professionals supervised by clinical psychologists provided guidance.

### Enhanced usual care

The psycho-educational intervention was based on the German S3-Guideline (14). It informed participants about the nature and evidence-based treatments of depression. The intervention mimicked and enhanced usual care as information were systematically offered that patients might not routinely receive from their GP. Participants could review the material as often as they wanted to. However, we did not monitor the actual uptake of the intervention. There was neither an online trainer involved in the intervention nor were any homework assignments given to participants.

## Outcomes

The primary outcome was time to onset of MDD in the intervention group relative to the control group over a 12-month follow-up period using DSM-IV criteria as assessed with the telephone-administered structured clinical interview for DSM-IV Axis Disorders (SCID) at 6- and 12-month follow-up covering the period to the previous assessment. Diagnostic interviews were conducted by psychologists trained in delivering the SCID. The inter-rater agreement of the Axis I disorders is moderate to excellent (16). The interformat reliability between face-to-face and telephone-administered SCIDs is considered to be excellent (17). To examine inter-rater reliability, interviews were audiotaped and second-rated by an independent, blind, experienced rater. The kappa coefficient for inter-rater agreement was 0.77 (based on data of 12% of the participants) indicating excellent agreement. In case of disagreement between the study interviewer and the independent rater, consensus was reached through discussion. Time to onset of MDD was assessed as accurately as possible using the Life Chart method as developed by Lyketsos in order to reduce a potential recall bias (18). In this method, age- and calendar-linked personal landmarks are used to assess the time sequence of i.e. depressive symptomatology and life events in parallel. During the interview the first day of a depressive episode was established. If the exact day could not be established, the closest week (month) was defined and the mid-point of that week (month) was used.

Secondary clinical outcomes were all based on self-report measures assessed online at 6- and 12-month follow-up and included depressive symptom severity (CES-D (10)), functional impairment (SF-12 (19)), anxiety (HADS-A (20)), problem-solving skills (SPSI-R (21)), behavioral activation (BADS-SF (22)), mastery (PSMS (23)), worrying (PSWQ (24)), insomnia severity (ISI (25)), and health care service uptake (TiC-P (15)).

## Statistical analysis

Because no estimate of clinical relevance exists for the incidence of major depressive disorder (MDD), we assumed an absolute risk reduction of at least 10% for the incidence of MDD

between intervention and control group as clinically relevant. This (normative) threshold was derived by 1) consulting clinical experts in the field of depression prevention and 2) asking stakeholders who would potentially use a web-based intervention in routine care (i.e. health insurance companies) about a threshold above which they would consider the results as worthwhile from a clinical perspective. Based on previous studies evaluating interventions directed at the prevention of MDD, we expected a mean incidence of MDD in the control group of 25% within the 12-month follow-up period (26, 27). A power calculation indicated that 406 participants were needed to demonstrate an absolute risk reduction of 10% between the conditions as statistically significant at $\alpha < 0.05$ (2-tailed) with a power of $(1-\beta) = 0.80$ using survival analysis while accounting for a 20% dropout (calculated using PASS 12). All analyses are reported according to the CONSORT statement (28). Analyses were based on intention-to-treat (ITT) meaning that all randomized participants were included in the analyses irrespectively of whether they adhered to the treatment protocol or not. Kaplan-Meier curves and Cox proportional hazard regression analyses were used to determine differences in time to onset of MDD (in weeks) between intervention and control group (29). The mean survival time was calculated as the area under the Kaplan-Meier survivor function within the 12-month trial period. Cox regression computes estimates of survival time for right-censored data. An observation is right-censored when a participant is no longer eligible to experience a depressive episode, i.e. the participant is lost-to-follow-up or completes the follow-up period without experiencing a major depressive episode. Time to onset of MDD was used as dependent variable and treatment condition as the independent variable covarying baseline depressive symptom severity (i.e. baseline CES-D sum score). Concurrent use of antidepressants was also included as covariate into the Cox proportional hazard model (post hoc). As the use of antidepressants was not a predictor of the outcome, it was excluded from the final model. The Cox model assumes that hazards are proportional implying that the effect of a given covariate does not change over time. We tested the proportional-hazards assumption based on the scaled Schoenfeld residuals test (30). Person-time based Poisson regression was used to obtain incidence rate ratios (IRRs). We calculated the number needed to treat (NNT) and 95% CIs to avoid one additional case of MDD as compared to the control group according to Altman and Andersen (31). In secondary analyses, analysis of covariance was used to compare outcomes between groups at 12-month follow-up adjusting for baseline scores to assess differences in secondary outcomes. The effects on secondary clinical outcomes at post-treatment and 6-month follow-up have been reported elsewhere (9). Missing data were imputed using multiple imputation techniques as implemented in Stata 13. In addition, per protocol analyses were conducted based on the sample of participants who adequately adhered to the intervention protocol (i.e. completing at

least five out of six intervention sessions). A significance level of .05 (two-sided) was used for all outcome analyses. All data was analyzed using Stata 13 for Windows (32).

## Sensitivity analyses

To test the robustness of the findings, missing data were imputed using imputation techniques for survival data as implemented in Stata 13 and the same Cox model as described in the main analyses was used. In addition, we tested the robustness of the findings by excluding those participants who revealed their randomization status during SCID follow-up interviews. To assess the robustness of the preventive effect of the intervention, a sub-group analysis was performed excluding those participants taking antidepressants at baseline. A per-protocol analysis was conducted to test whether intervention completers (i.e., completing at least 5 out of 6 intervention sessions) differed from non-completers a) with regard to any baseline characteristics, and b) with regard to time to onset of a major depressive disorder.

# Results

## Participant characteristics

Between March 15, 2013 and March 4, 2014, 406 participants were enrolled in the study (intervention group n = 202; control group n = 204). Overall, 335 participants (82%) participated in the SCID/DSM-IV follow-up interviews (69 participants were censored at baseline, two participants at 6-month follow-up) (Figure 1). There were no significant differences in follow-up rates between study conditions [$\chi^2$ (1, n = 406) = 1.49, p = .22]. Dropout was not associated with baseline depressive symptom severity or any socio-demographic factor. Figure 1 shows the flow of participants through the study. Some participants (n = 17, 5.1%), informed interviewers about their randomization status during the SCID follow-up interviews (10 in the intervention group; 7 in the control group). The probability that interviewers correctly guessed a participant's randomisation status was 53%. Participant characteristics at baseline are described in detail elsewhere (9) and shown in Table 1. In brief, the modal participant was female, Caucasian, 45 years of age with an above average level of education, and employed.

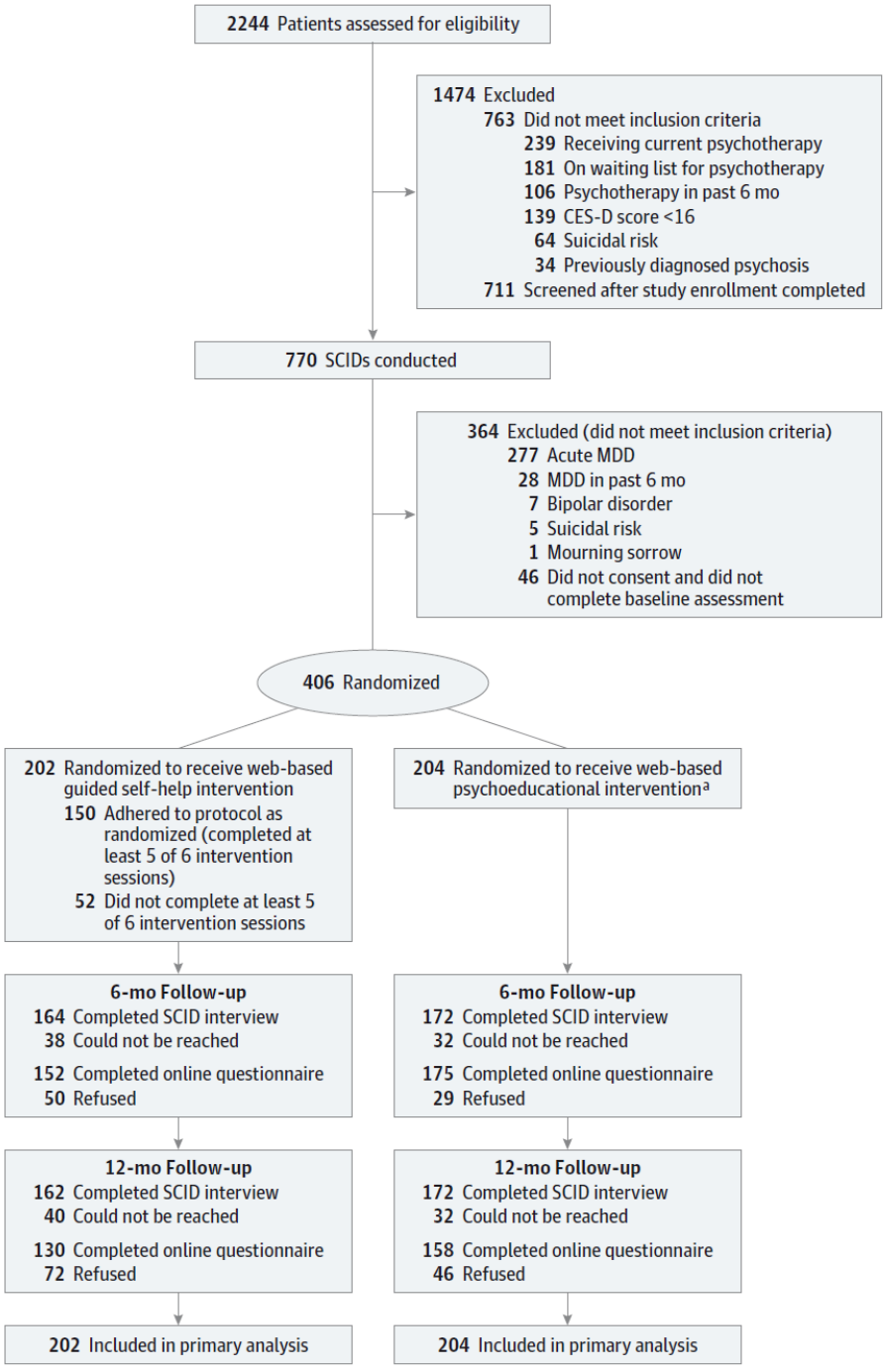


**Figure 1.** Assessment, randomization, and follow-up of study participants

**Table 1.** Baseline characteristics of participants according to study group

| Characteristic | Intervention group (n=202) | Control group (n=204) | Total sample (N=406) |
|---|---|---|---|
| **CES-D sum score, mean (SD)** | 26.25 (7.85) | 26.42 (7.99) | 26.34 (7.91) |
| **Age, mean (SD)** | 45.71 (11.93) | 44.38 (11.84) | 45.04 (11.89) |
| **Gender, n (%)** | | | |
| **Male** | 53 (26.2) | 53 (26) | 106 (26.1) |
| **Female** | 149 (73.8) | 151 (74) | 300 (73.9) |
| **Relationship, n (%)** | | | |
| **Single** | 62 (30.7) | 67 (32.8) | 129 (31.8) |
| **Married or cohabiting** | 102 (50) | 107 (52.9) | 209 (51.5) |
| **Divorced or separated** | 37 (18.3) | 25 (12.3) | 62 (15.3) |
| **Widowed** | 2 (1) | 4 (2) | 6 (1.5) |
| **Ethnicity, n (%)** | | | |
| **Caucasian** | 165 (81.2) | 174 (85.8) | 339 (83.5) |
| **Black** | 1 (0.5) | 0 | 1 (.2) |
| **Hispanic** | 0 | 1 (0.5) | 1 (.2) |
| **Not reported** | 37 (18.3) | 28 (13.7) | 65 (16) |
| **Level of education, n (%)** | | | |
| **Low (primary)** | 5 (2.5) | 3 (1.5) | 8 (2) |
| **Middle (secondary)** | 33 (16.3) | 34 (16.7) | 67 (16.5) |
| **High (A-level or higher)** | 164 (81.2) | 167 (81.9) | 331 (81.5) |
| **Employment status, n (%)** | | | |
| **Full time working** | 105 (52) | 106 (52) | 211 (52) |
| **Part time working** | 65 (32.2) | 59 (28.9) | 124 (30.5) |
| **Non-working** | 26 (12.4) | 28 (14.2) | 54 (13.3) |
| **Unemployed or seeking work** | 4 (2) | 8 (3.9) | 12 (3) |
| **On sick leave** | 3 (1.5) | 2 (1) | 5 (1.2) |
| **Income in Euro, n (%)** | | | |
| **Low (< 10.000)** | 16 (7.9) | 25 (12.3) | 41 (10.1) |
| **Middle (10 - 60.000)** | 145 (71.8) | 149 (73) | 294 (72.4) |
| **High (> 60.000)** | 26 (12.9) | 12 (5.9) | 38 (9.4) |
| **Not reported** | 18 (8.8) | 15 (7.4) | 33 (8.1) |
| **Previous** | | | |
| **Psychotherapy, n (%)** | 88 (43.6) | 88 (42.2) | 176 (43.4) |
| **Health training, n (%)** | 51 (25.2) | 45 (22.1) | 96 (23.6) |
| **Use of antidepressants, n (%)** | 50 (24.8) | 44 (21.6) | 94 (23.2) |
| **Way of recruitment** | | | |
| **Health insurance company, n (%)** | 91 (45) | 94 (46.1) | 185 (45.6) |
| **Press articles or internet search, n (%)** | 70 (34.7) | 73 (35.8) | 143 (35.2) |
| **Not known** | 41 (20.3) | 37 (18.1) | 78 (19.2) |

Abbreviations: CES-D, Center for Epidemiologic Studies Depression Scale; SD, standard deviation; Level of education, elementary school, high school, A-level examinations ("Abitur") or above (university degree); income, yearly gross income

## Effectiveness of intervention

The average treatment duration was 5.84 weeks (SD = 4.37). On average, participants completed 4.93 out of 6 sessions (9). The total time a trainer spent per participant was approximately three hours. The Kaplan-Meier survival curves for the intervention and control group generated for the 12-months study period are shown in Figure 2. The Kaplan-Meier estimates of the cumulative incidence of MDD were 34% (95% confidence interval [CI] 28 - 42) for the intervention and 49% (95% CI 42 - 57) for the control condition. The corresponding person-time based incidence rate ratio (IRR) was 0.60 (95% CI 0.42 - 0.84, p = .003). The log-rank test showed a statistically significant difference between incidence rates over time (p = .004 by the log-rank test).

The mean time to onset of MDD within the 12-month trial period in intervention and control group was 42 weeks (95% CI 40 - 45) and 36 weeks (95% CI 34 - 39), respectively. Cox regression, which controlled for baseline depressive symptom severity, showed a hazard rate [HR] of 0.59 (95% CI 0.42 - 0.82, p = .002). The estimated hazard ratio for depressive symptom severity was 1.06 (95% CI 1.04 - 1.08, < .001). There was no evidence for non-constant hazard ratios (global test of non-proportionality p = .97; treatment condition p = .90; depressive symptom severity p = .84). At 12-month follow-up, the number needed to treat to avoid one new case of MDD was 5.9 (95% CI 3.9 - 14.6).

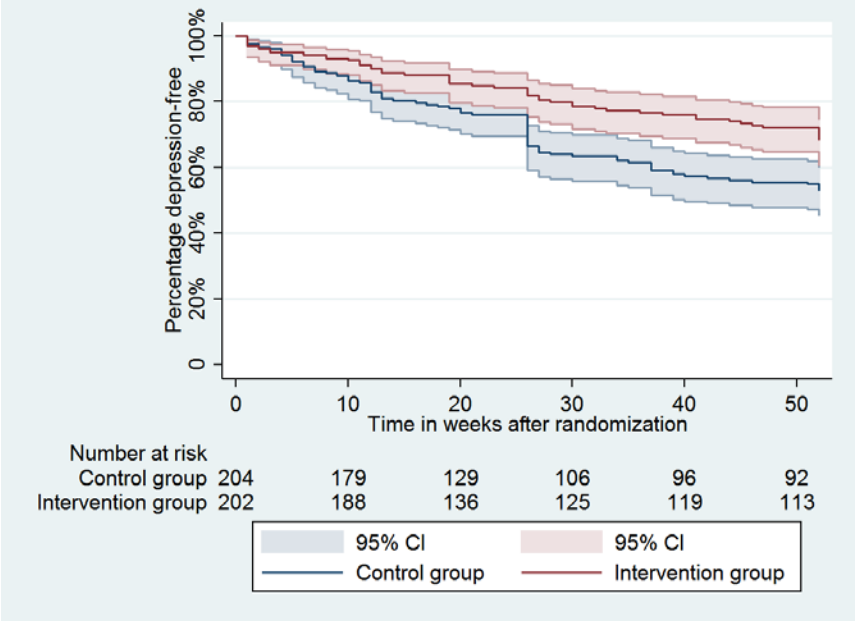


**Figure 2.** Kaplan-Meier survival estimates illustrating time to onset of MDD by study group

## Secondary outcomes

Table 2 shows means, standard deviations, and between-group effect sizes of secondary clinical outcomes at follow-up assessments based on the intention-to-treat sample. Significant differences in change from baseline to 12-month in favor of the intervention group were found for all outcomes except for the physical health summary score of the SF-12, the positive problem-orientation subscale of the SPSI-R, and worrying. Corresponding effect sizes were small to moderate (Table 2). We did not find any significant differences in mental health care use (i.e. out-patient care, in-patient care, or use of antidepressants) between study conditions (Table 3).

## Sensitivity analyses

In the sensitivity analysis using imputed data instead of censoring for missing values, Cox regression, again controlling for baseline depressive symptom severity, revealed a hazard ratio of 0.65 (95% CI 0.49 - 0.86; p = .002). Excluding those participants taking antidepressant at baseline or who revealed their randomization status during the SCID interview showed similar hazard ratios as compared to the main analysis. Intervention completers were slightly older and better educated, and rather female than intervention non-completers. Cox regression, controlling for baseline depressive symptom severity, revealed a hazard ratio of 0.71 (95% CI 0.46 - 1.10, p = .13).

**Table 2.** Means (95% CI) and between-group effect sizes for each secondary clinical outcome measure and measurement based on the intention-to-treat sample (N = 406)

| | **Baseline assessment** | | **12-month FU** | | **Between-group effect size Cohen's d (95% CI)** |
|---|---|---|---|---|---|
| | mean | 95%CI | mean | 95%CI | Baseline-12-month FU |
| **CES-D** | | | | | 0.29 (0.09 - 0.04) |
| **INT** | 26.26 | 25.17 - 27.35 | 16.84 | 15.69 - 17.99 | |
| **CTR** | 26.42 | 25.32 - 27.53 | 19.42 | 18.08 - 20.76 | |
| **SF-12 MCS** | | | | | 0.37 (0.17 - 0.56) |
| **INT** | 31.45 | 30.39 - 32.43 | 43.50 | 42.22 - 44.80 | |
| **CTR** | 30.77 | 29.57 - 31.76 | 39.86 | 38.40 - 41.32 | |
| **SF-12 PCS** | | | | | 0.07 (-0.12 - 0.26) |
| **INT** | 47.47 | 46.12 - 48.82 | 48.42 | 47.31 - 49.52 | |
| **CTR** | 47.83 | 46.53 - 49.03 | 47.86 | 46.76 - 48.96 | |
| **HADS-A** | | | | | 0.34 (0.15 - 0.54) |
| **INT** | 9.59 | 9.14 - 10.05 | 6.63 | 6.17 - 7.09 | |
| **CTR** | 9.59 | 9.12 - 10.01 | 7.83 | 7.33 - 8.33 | |
| **BADS-SF** | | | | | 0.34 (0.14 - 0.53) |
| **INT** | 25.45 | 24.37 - 26.53 | 33.93 | 32.84 - 35.03 | |
| **CTR** | 24.62 | 23.57 - 25.66 | 31.25 | 30.14 - 32.37 | |
| **SPSI-NPO** | | | | | 0.14 (-0.06 - 0.33) |
| **INT** | 7.00 | 6.38 - 7.61 | 5.32 | 4.79 - 5.86 | |
| **CTR** | 6.99 | 6.34 - 7.63 | 5.87 | 5.31 - 6.42 | |
| **SPSI-PPO** | | | | | 0.09 (-0.11 - 0.28) |
| **INT** | 9.12 | 8.57 - 9.67 | 11.33 | 10.87 - 11.79 | |
| **CTR** | 9.18 | 8.68 - 9.68 | 11.04 | 10.59 - 11.49 | |
| **PSWQ** | | | | | 0.16 (-0.04 - 0.35) |
| **INT** | 9.44 | 8.88 - 10.00 | 6.49 | 5.91 - 7.07 | |
| **CTR** | 9.76 | 9.22 - 10.30 | 7.17 | 6.56 - 7.77 | |
| **ISI** | | | | | 0.15 (-0.05 - 0.34) |
| **INT** | 12.00 | 11.19 - 12.80 | 8.85 | 8.14 - 9.57 | |
| **CTR** | 11.70 | 10.88 - 12.51 | 9.64 | 8.88 - 10.34 | |

**Table 2.** Means (95% CI) and between-group effect sizes for each secondary clinical outcome measure and measurement based on the intention-to-treat sample (N = 406) (continued)

| | **Baseline assessment** | | **12-month FU** | | **Between-group effect size Cohen's d (95% CI)** |
|---|---|---|---|---|---|
| **PSMS** | | | | | 0.14 (-0.05 - 0.33) |
| **INT** | 19.11 | 18.64 - 19.59 | 20.80 | 20.33 - 21.27 | |
| **CTR** | 19.22 | 18.81 - 19.63 | 20.33 | 19.87 - 20.79 | |

Abbreviations: CES-D, Centre for Epidemiologic Studies Depression Scale; SF-12 MCS, SF-12 mental health summary score; SF-12 PCS, SF-12 physical health summary score; HADS-A, Hospital Anxiety and Depression Scale, anxiety subscale; BADS-SF, Behavioral Activation for Depression Scale – Short Form; SPSI-NPO, Social Problem Solving Inventory-Revised, Negative Problem Orientation Subscale; SPSI-PPO, Social Problem Solving Inventory-Revised, Positive Problem Orientation subscale; PSWQ, Penn State Worrying Questionnaire, ultra-brief form; ISI, Insomnia Severity Inventory; PSMS, Pearlin and Schooler Mastery Scale; INT, intervention group (n = 202); CTR, control group (n = 204); 6-month FU, 6-month follow-up; 12-month FU, 12-month follow-up; 95% CI, 95% confidence interval

**Table 3.** Health care service use during 12-month follow-up period by study condition

| | **Intervention group** | | **Control group** | | **Differences in percentages between study conditions[c] (95% CI)** | |
|---|---|---|---|---|---|---|
| | 6-month FU[a] (n = 152) | 12-month FU[b] (n = 130) | 6-month FU (n = 175) | 12-month FU (n = 158) | 6-month FU | 12-month FU |
| **GP** | 96 (63.2%) | 79 (60.8%) | 88 (50.3%) | 83 (52.5%) | 12.9% (2 - 23) | 8.3% (-3 - 19) |
| **Psychotherapist** | 6 (3.9%) | 10 (7.7%) | 17 (9.7%) | 12 (7.6%) | 5.8% (-1 - 11) | 0.1% (-6 - 7) |
| **Antidepressants** | 32 (21.1%) | 27 (20.8%) | 40 (22.9%) | 43 (27.2%) | 1.8% (-7 - 11) | 6.4% (-4 - 16) |
| **Neurologist** | 11 (7.2%) | 10 (7.7%) | 9 (5.1%) | 8 (5.1%) | 2.1% (-3 - 8) | 2.6% (-3 - 9) |
| **Psychiatrist** | 3 (2%) | 2 (1.5%) | 8 (4.6%) | 6 (3.8%) | 2.6% (-2 - 7) | 2.3% (-2 - 7) |
| **Specialist in psychosomatic medicine** | 0 | 1 (0.8%) | 1 (0.6%) | 2 (1.3%) | 0.6% (-2 - 3) | 0.5% (-3 - 4) |

Abbreviations: GP, General Practitioner; 95% CI, 95% confidence interval; FU, follow-up

[a]6-month follow-up covering the previous three months as measured with the TiC-P (Trimbos/iMTA questionnaire for Costs associated with Psychiatric illness)

[b]12-month follow-up covering the previous three months as measured with the TiC-P

[c]based on Newcombe RG. Interval Estimation for the Difference Between Independent Proportions: Comparison of Eleven Methods. Statistics in Medicine. 1998;17:873.

# Discussion

We examined whether a web-based guided self-help intervention was effective in preventing the onset of diagnosed MDD when compared to enhanced usual care over a 12-month follow-up period in people experiencing sub-threshold depression. Results of the study suggests that the intervention could effectively reduce the risk of MDD onset, or at least delay its onset.

The incidence of MDD in the control group was remarkably higher than what is usually found in prevention studies (6). The possibly substantial secondary prevention population may have been a reason for the high rate of MDD in the control group. However, some prevention studies assessed only current MDD at follow-ups, hence not covering the whole study time frame (26, 33). The hazard ratio of 0.59 (95% CI 0.42 - 0.82) found in this study compares favorably to results from other indicated prevention studies focusing on an adult population without additional risk factors. To our knowledge, only two of such studies on non-web-based interventions have been conducted so far, revealing mixed results with IRRs ranging from of 0.66 (95% CI 0.40 - 1.09) (34) to 1.07 (95% CI 0.57 - 2.01) (35). Results of the presented study are also comparable to preventive effects of psychological interventions in at-risk populations (i.e., HR = 0.60, 95% CI 0.31 - 1.16 in physically ill patients) (36). Indicated preventive interventions could thus be targeted also at populations without additional risk indicators to result in clinically relevant effects. Considering the high incidence rate in the control group, the intervention might attract particularly those participants with an elevated risk of developing MDD.

The present study may have implications for clinical practice and research. Firstly, to our knowledge, this trial is the largest prevention trial conducted so far and it supports the effectiveness of indicated preventive interventions. Secondly, the NNT of 5.9 found in this study is comparable to NNTs in the treatment of MDD (37). It implies that of those identified with sub-threshold depression and participating in the intervention almost 15% would benefit in terms of a prevented episode of MDD within a 12-month period. Thirdly, of those who developed MDD within the 12-month trial period, the onset of MDD was delayed in the intervention group as compared to the control condition. Although preventing the onset of depressive episodes is preferable as it results in complete avoidance of disease burden, delaying the onset of MDD is also important. Every year in which new cases of MDD could be avoided will both result in considerably less pain (i.e. the patient himself and also his family) and reduced economic costs. Fourthly, this study revealed that reducing the incidence of MDD is also possible using a web-based guided self-help intervention. Fifthly, web-based interventions might attract people who may not use face-to-face interventions. Less burdensome interventions are needed as the majority of individuals experiencing depressive symptoms does not seek help (38) and

participation rates in face-to-face interventions for sub-threshold depression are low (39). Delivering low-threshold evidence-based preventive interventions via the Internet may be a strategy with potential to reach individuals at an early stage and may help to prevent the transition from sub-threshold depression to a full-blown depressive disorder or relapses in recurrent depressive disorder. However, the applicability of web-based interventions is related to (a) the acceptance of such interventions by the target population (i.e. preferences for different treatment modalities, such as face-to-face interventions) and (b) the availability of technical requirements (i.e. reliable access to the Internet).

However, this study has some limitations. Firstly, in this study, we did not assess lifetime history of MDD at baseline meaning that the results of this study refer to a mixed sample of first depression onsets and depression recurrences. The incidence rate in the control group was higher than one could expect if predominantly participants without lifetime history of depression were included. Thus, we cannot conclude whether results can independently be generalized to both first depression onset and prevention of recurrence. Future studies should thus clarify whether web-based guided self-help interventions are effective both for the prevention of first depression onset and the prevention of recurrence. Secondly, the time horizon of this study was limited to 12 months. Thirdly, a block randomization of size two was used. It would appear that a randomization block of size two assures that whoever did the randomization knew in advance the allocation of half of the participants. However, the randomization procedure was performed in order of incoming informed consent forms and collecting informed consent forms and randomizing participants were performed by two independent researchers under procedures designed to keep the concealment of the allocation intact. Fourthly, we assumed a 10% absolute risk reduction as clinically relevant. However, this assumption was based on expert opinion. Fifthly, we did not assess (chronic) medical conditions. Experiencing (chronic) medical conditions might be a risk indicator for the onset of a major depressive disorder. Future studies should thus assess such conditions or evaluate the effects of web-based guided self-help interventions directly in such patient groups, respectively. Sixthly, it was not possible to mask participants to the study condition they were assigned to. This is a common problem in trials evaluating psychological interventions. Nevertheless, it might have distorted results of the trial. Seventhly, not all individuals may benefit from this particular web-based intervention to the same degree. Future studies should investigate potential effect modifiers (i.e. internet literacy). Eighthly, usual care was not standardized across GPs. As GPs were not known to us, we could not adjust for GP in the analyses. Ninthly, participants in this study were better educated than the general population and predominately female. Conclusions drawn from the present study may therefore not generally apply to other populations. However, we used in this trial an open recruitment strategy mimicking the way

how people will be recruited for e-health interventions in the future, thus providing ecological validity to the current study and the sample on which it is based. Tenthly, although the control group got access to a web-based psychoeducational intervention, the study conditions were not balanced with regard to human support. This was chosen as we wanted to evaluate the effects of the intervention compared to care-as-usual, the usual comparator in pragmatic trials aiming to achieve high ecological validity (40). However, we cannot rule out that part of the observed preventive effect is caused by human attention. Additionally, the use of antidepressant medication was not an exclusion criterion. As we excluded those participants with a major depressive disorder in the previous six months, we assumed that we did not include participants in the study who were treated for depression. However, we cannot rule out that for some participants the web-based intervention was an adjunct to concurrent antidepressant treatment (i.e. secondary prevention). Also, we did not measure the uptake of the web-based psychoeducational intervention. Future studies should investigate a possible dose-effect relationship. Eleventh, some unguided web-based interventions for depressive symptoms have been shown to be possibly ineffective (41). Because the intervention in this study relied on the use of online trainers, it is therefore possible that unguided web-based interventions would be less effective or ineffective. Studies are needed to evaluate the preventive effects of unguided web-based interventions on the onset of major depressive disorder.

# Conclusions

Among patients with sub-threshold depression, the use of an indicated web-based guided self-help intervention compared to usual care reduced the incidence of major depressive disorder over 12 months. Further research is needed to understand whether the effects are generalizable to both first depression onset and depression recurrence as well as efficacy without the use of an online trainer.

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