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Heterogeneity of Treatment Effects in Internet- and Mobile-Based Interventions for Depression

A Systematic Review and Meta-Analysis

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Abstract

IMPORTANCE While the effects of internet- and mobile-based interventions (IMIs) for depression have been extensively studied, no systematic evidence is available regarding the heterogeneity of treatment effects (HTEs), indicating to what extent patient-by-treatment interactions exist and personalized treatment models might be necessary.

OBJECTIVE To investigate the HTEs in IMIs for depression as well as their efficacy and effectiveness.

DATA SOURCES A systematic search in Embase, MEDLINE, Central, and PsycINFO for randomized clinical trials and supplementary reference searches was conducted on October 13, 2019, and updated March 25, 2022. The search string included various terms related to digital psychotherapy, depression, and randomized clinical trials.

STUDY SELECTION Titles, abstracts, and full texts were reviewed by 2 independent researchers. Studies of all populations with at least 1 intervention group receiving an IMI for depression and at least 1 control group were eligible, if they assessed depression severity as a primary outcome and followed a randomized clinical trial (RCT) design.

DATA EXTRACTION AND SYNTHESIS This study followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses reporting guidelines. Risk of bias was evaluated using the Cochrane Risk of Bias Tool. HTE was investigated using logarithmic variance ratios (lnVR) and effect sizes using Hedges *g*. Three-level bayesian meta-regressions were conducted.

MAIN OUTCOMES AND MEASURES Heterogeneity of treatment effects was the primary outcome of this study; magnitudes of treatment effect sizes were the secondary outcome. Depression severity was measured by different self-report and clinician-rated scales in the included RCTs.

RESULTS The systematic review of 102 trials included 19 758 participants (mean [SD] age, 39.9 [10.58] years) with moderate depression severity (mean [SD] in Patient Health Questionnaire-9 score, 12.81 [2.93]). No evidence for HTE in IMIs was found (lnVR = −0.02; 95% credible interval [CrI], −0.07 to 0.03). However, HTE was higher in more severe depression levels ($\hat{\beta}$ = 0.04; 95% CrI, 0.01 to 0.07). The effect size of IMI was medium (*g* = −0.56; 95% CrI, −0.46 to −0.66). An interaction effect between guidance and baseline severity was found ($\hat{\beta}$ = −0.24, 95% CrI, −0.03 to −0.46).

CONCLUSIONS AND RELEVANCE In this systematic review and meta-analysis of RCTs, no evidence for increased patient-by-treatment interaction in IMIs among patients with subthreshold to mild depression was found. Guidance did not increase effect sizes in this subgroup. However, the

(continued)

Key Points

Question Is there evidence from randomized clinical trials (RCTs) that patients respond differently to internet- and mobile-based interventions (IMIs) for depression?

Findings In this meta-analysis of 102 RCTs involving 19 758 participants, clinically relevant effect sizes for unguided IMIs in patients with subthreshold to mild depression without evidence for substantial patient-by-treatment interaction was found. In contrast, heterogeneity of treatment effects and moderating effects of guidance increased with baseline depression severity.

Meaning These findings suggest that moderate improvements in subthreshold to mild depression can be reasonably expected from unguided IMIs, but individuals with more severe depression could respond differently, indicating the need for digital precision psychotherapy and future research in this subgroup.

+ Supplemental content

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Abstract (continued)

association of baseline severity with HTE and its interaction with guidance indicates a more sensitive, guided, digital precision approach would benefit individuals with more severe symptoms. Future research in this population is needed to explore personalization strategies and fully exploit the potential of IMI.

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Introduction

Major depression constitutes one of the leading causes of disease burden worldwide, with a global prevalence of 3.2% (95% CI, 2.7%-3.7%) and 49.4 (95% CI, 33.6-68.7) million disability-adjusted life-years worldwide in 2020.[1-3] Besides the high personal burden for affected individuals, depression is related to high economic costs and increased risk for chronic diseases and mortality, further highlighting the need for effective depression treatment.[4-7] In addition to pharmacological therapy[8] and face-to-face psychotherapy for depression,[9,10] internet- and mobile-based interventions (IMIs) have been frequently studied in the last 2 decades.[11,12]

IMIs transfer face-to-face psychotherapeutic approaches into the virtual space providing time- and location-independent access to treatment.[11-13] Typically, they present web-based programs with segmented modules, often organized into weekly sessions (eg, psychoeducation, problem-solving, activity activation).[11] More recently, mobile health applications have also been studied.[11,14] Besides their technical setup, IMIs primarily hinge on cognitive behavioral therapy (CBT) and differ in the level of human support, ranging from unguided approaches (ie, completely standardized treatment protocols without human involvement) to guided interventions with human therapeutic guidance (eg, e-coach feedback on exercises or recommendations for actions).[11,15,16]

A recent meta-analysis of randomized clinical trials (RCTs)[11] indicated an overall effect size (ES) of IMIs of g = 0.52 (95% CI, 0.43-0.60) for depression severity. Subgroup analysis in a smaller set of pragmatic effectiveness trials also showed effectiveness, with g = 0.30 (95% CI, 0.15-0.45).[11] The few studies comparing IMI with traditional face-to-face psychotherapy showed comparable effects.[8,17-20] This evidence strongly suggests that IMIs are an effective treatment for depression.[11] However, whether IMIs have consistent effects for all individuals or whether there is substantial heterogeneity of treatment effects (HTE) is an open question, potentially with implications for precision psychotherapy.[11,12,16,21]

HTE can be systematically investigated by analyzing RCTs using the following rationale[22-24]: in an RCT, randomly assigning participants to a control (CG) or an intervention group (IG) eliminates casual differences between the groups. Hence, the severity means and variance in the IG and the CG are equivalent after randomization. In the case of an effective intervention, the means in the IG and the CG are different after treatment. Similarly, the variance ratio can be investigated. If there is more variance in the individual responses in the IG compared with the CG, this provides evidence for the presence of subgroups responding differently to the intervention (eAppendix 1 in Supplement 1). Hence, a meta-analysis on the variance ratios between IG and CG reported in RCTs can evaluate whether higher individual responses and substantial HTE are systematically occurring for a treatment type compared with control conditions. A greater extent of unequal variance would imply stronger evidence for the presence of meaningful patient-by-treatment interaction.[22-24]

HTE in meta-analyses was initially studied in other health conditions[24-26] and, more recently, in pharmacological treatments and face-to-face therapy for depression.[23,27] In depression treatment, antidepressants do not show substantial HTE, indicating that they are an effective treatment option without substantial variations in effectiveness compared with treatment as usual or other control groups.[23] In contrast, face-to-face psychotherapy shows HTE, indicating the presence of subgroups that respond particularly well to it and to specific treatment types (eg, behavioral activation therapy or cognitive-behavioral therapy).[27] Hence, optimizing face-to-face psychotherapy by identifying

well-responding subgroups and tailoring (eg, by selecting treatment type or taking known moderators into account, like depression episode number, duration, and severity) can mark an important step toward improved psychotherapy.[27-30]

Given that IMIs usually transfer existing face-to-face psychotherapeutic approaches to a digital platform, the question arises whether the evidence for systematic patient-by-treatment interactions transfers to IMIs or is eliminated (eg, through the high standardization of treatment protocols in IMIs). In the case of equivalent variances between IG and CG, we could reasonably assume the average meta-analytical ES of IMIs for the individual. In contrast, substantial HTE would provide evidence that only certain subgroups respond to IMIs, indicating a potential need for digital precision psychotherapy.

In this study, we systematically review and analyze RCTs on IMIs for depression to provide evidence of whether substantial HTE exists. Additionally, we extend previous findings on the ES of IMIs for depression with a primary interest in the role of guidance, baseline severity, and evidence for effectiveness beyond highly controlled laboratory settings.[11,12,31,32]

Methods

Study Design and Search Strategy

The present study is a systematic review and meta-analysis of the HTE of IMIs for depression and extends a previous analysis on the efficacy and effectiveness of IMIs for depression.[11] We searched the literature databases Embase, MEDLINE, Central, and PsycINFO for relevant articles. The original search was conducted on October 13, 2019, and updated for the present study on March 25, 2022. The complete search string can be found in eAppendix 2 in Supplement 1. Second, we reviewed the reference lists of previous systematic reviews.[11] Lastly, we performed a backward search in the reference list of all included studies. All procedures have been registered in the open science framework.[33] We followed the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA)[34] guidelines for reporting systematic reviews in the present study.

Inclusion Criteria and Data Extraction

We applied the following predefined population, intervention, comparator, outcome, and study design (PICOS) inclusion criteria:

- Population: studies with participants of all ages with depressive symptoms were included, and all genders, nationalities, and cultural backgrounds were eligible;
- Intervention: studies needed to apply at least 1 IMI for depression (ie, computer-, online-, internet-, web-, or smartphone-based intervention), and the IMI could be provided online or offline;
- Comparison: IG(s) needed to be compared against at least 1 CG, and both inactive (eg, waiting list CG) and active (eg, treatment as usual) CGs were eligible;
- Outcomes: depression severity must have been included and measured by a validated self- or clinician-rated depression scale;
- Study design: to be included, studies needed to follow an RCT design and all studies needed to be approved by an institutional review board or ethics committee and have obtained informed consent from their participants.

For the coding and data extraction, 2 independent researchers assessed each included study (2 of Y.T., L.B.S., I.M., and P.P.). Participant characteristics (eg, mean age), design aspects (eg, type of control group), intervention details (eg, guidance), and method features (eg, missing data handling) were extracted. All disagreements in data extraction were resolved in discussion, and the required data (eg, variance ratios and ESs) for analyses could be obtained for all included studies.

Risk of Bias

We used the Cochrane Risk of Bias Tool I to assess study quality.[35] Accordingly, the risk of bias was rated as low, unclear, or high on the 7 sources of bias: (1) random sequence generation, (2) allocation

concealment, (3) blinding of participants and personnel, (4) blinding of outcome assessment, (5) incomplete outcome data, (6) selective reporting, and (7) other. In principle, blinding of participants and personnel in psychotherapeutic research is not feasible.[36] Hence, we have rated all self-report instruments (answered by unblinded participants) in the domain of blinding of outcome assessors as having high risk of bias.

Statistical Analysis

HTE of IMIs for Depression

We followed the procedures of previous analyses in the context of pharmacological and psychotherapeutic interventions for depression and conducted a 3-level bayesian random-effects meta-regression.[23,27,37] The primary outcome was the logarithmic variance ratio (lnVR) of depression severity between IG and CG (level 1) at post assessment while allowing for differences between outcomes within a study (level 2, eg, multiple depression outcomes or CGs) and between studies (level 3). Hence, the level 1 estimate provides an estimate of the extent the variances in the IG and CG differ. A positive estimate indicates higher variance in the IG compared with CG and would provide meta-analytical evidence for substantial patient-by-treatment interaction and patients responding differently to IMIs compared with control conditions.[22,23,27] For further details on model parameters, see eMethods 1 in Supplement 1. To avoid bias through a possible mean-variance relationship, we controlled for differences in mean scores by including the logarithm of the posttreatment severity mean ratio (lnER) from the IG to the CG.[22,23,27] We selected weak priors in all analyses (eMethods 2 in Supplement 1).

HTE Sensitivity and Subgroup Analysis

We conducted sensitivity and subgroup analyses to investigate the role of various design and study characteristics (ie, effectiveness and efficacy settings and control types), intervention characteristics (ie, guidance, therapeutic background, and delivery format), participant characteristics (ie, age, gender, and baseline severity), potential long-term HTE, year of publication, assessment time, and risk of bias. eMethods 3 in Supplement 1 includes coding and analysis details. Subgroup analyses were only conducted for subgroups with at least 10 studies.[27]

Secondary Analysis on ESs of IMI for Depression

Analogous to the HTE analysis, we conducted secondary analyses on the ESs of IMI on depression severity (Hedges *g*) using bayesian 3-level meta-regression (eMethods 4 in Supplement 1). Analyses included subgroup and moderation analyses (eg, guidance, baseline severity, or setting) as outlined in eMethods 3 in Supplement 1.

Software

The statistical software R version 4.2.2 (R Project for Statistical Computing) was used for all analyses. The R packages rstan[38] and brms[39] were used as the core package for the analysis. eAppendix 3 in Supplement 1 provides an overview of all packages. Analysis code and used data are freely available.[40]

Results

Study Characteristics

We included 102 trials[17-19,41-144] comprising a total of 19 758 participants with a mean (SD) age of 39.9 (10.58) years, a mean (SD) percentage of female participants of 69.13% (12.22), and moderate depression severity across the studies (mean [SD] Patient Health Questionnaire–9 score, 12.81 [2.93]). The PRISMA flowchart and more information about the dataset can be found in eAppendices 4 and 5 in Supplement 1 and the eTable in Supplement 2. The included trials were predominantly conducted in Europe (61 [59.80%]), followed by Canada and the United States (17 [16.67%]),

Australia and New Zealand (16 [15.69%]), and Asia (8 [7.84%]). Most studies investigated the efficacy of IMIs (78 [76.47%]) and compared IMIs with waiting list CGs (47 [44.76%]), followed by treatment as usual (27 [25.71%]), attention control (24 [22.86%]), face-to-face psychotherapy (6 [5.71%]), and 1 other (0.98%).[84] IMIs were based on cognitive behavioral therapy (71 [68.27%]) most frequently (third-wave therapy: 14 [13.46%]; problem-solving-therapy: 8 [7.69%]; psychodynamic therapy: 1 [0.98%]; life review therapy: 1 [0.98%]; other (eg, combined approaches): 9, [8.65%]). Therapeutic support by humans was provided in 56 studies (51.85%), while technical guidance was used in 27 (25.00%), and no guidance in 25 (23.15%). Internet-based interventions were most frequent (88 [86.27%]), followed by smartphone app–based interventions (6 [5.88%]), computer-based interventions (5 [4.90%]), and interventions combining internet and smartphone app (3 [2.94%]).

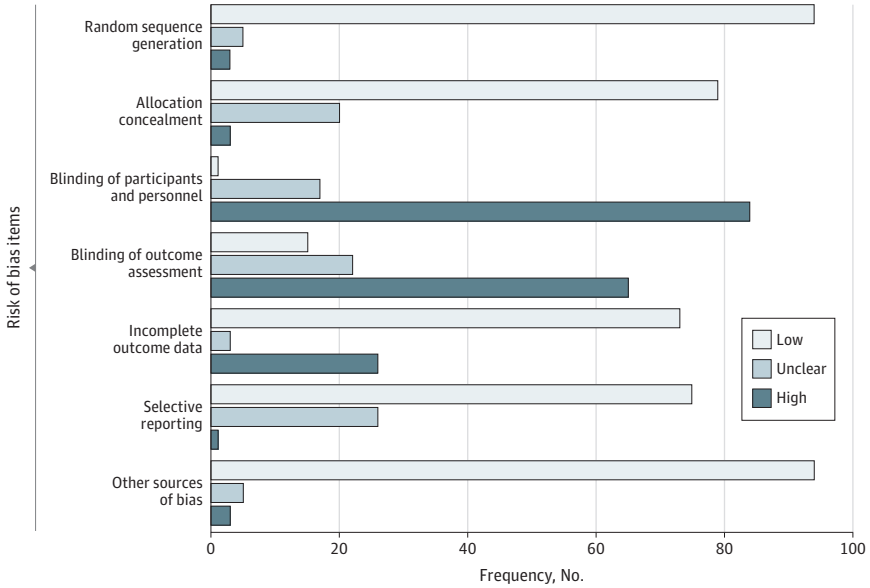
Risk of Bias and Study Quality

Most studies (94 [91.18%]) showed a low risk of bias in sequence generation (unclear: 5 [4.9%]; high: 3 [2.94%]). Allocation concealment was low in 79 studies (77.45%), unclear in 20 (19.61%), and high in 3 (2.94%). Blinding of participants was the domain with the highest risk of bias: 1 study was rated as low (0.98%), 17 (16.67%) as unclear, and 84 (82.35%) as high. Outcome assessors were not masked in 65 studies (63.73%), indicating a high risk of bias; risk of bias was unclear in 22 (21.57%) and low in 15 (14.71%). Of the 93 included studies (91.12%) that followed an intention-to-treat analysis, 70 (75.27%) applied adequate missing data handling. Overall bias due to incomplete outcome data was rated as low in 73 (71.47%), unclear in 3 (2.94%), and high in 26 (25.49%). Regarding selective reporting, only 1 study (0.98%) was rated as high, while 75 (73.53%) were rated low and 26 (25.49%) unclear. Analogous to sequence generation, other sources of bias were mostly low (94 [92.16%]; unclear: 5 [4.9%]; high: 3 [2.94%]) (**Figure**). Study-wise risk of bias ratings are reported in eAppendix 6 in Supplement 1. Sensitivity analysis on study quality did not affect results meaningfully (eAppendix 7 in Supplement 1).

HTE in IMI for Depression

The 102 included studies provided 153 comparisons between IG and CG at post treatment. The primary analysis of HTE in IMI at post treatment yielded no significant difference in variance ratios (level 1: lnVR = −0.02; 95% credible interval [CrI], −0.07 to 0.03). Level 2 (lnVR = 0.09; 95% CrI,

Figure. Summary of Risk of Bias Ratings According to the Cochrane Risk of Bias I Tool



0.05 to 0.13) and level 3 estimates (lnVR = 0.07; 95% CrI, 0.01 to 0.12) confirmed the 3-level analysis model.

The only significant variable associated with HTE was baseline severity ($\hat{\beta}$ = 0.04; 95% CrI, 0.01 to 0.07), indicating higher HTE in populations with greater depression severity. All other sensitivity and subgroup analyses showed a near-constant ES throughout the investigated study design, intervention, and participant characteristics (**Table**). Extended results can be found in eAppendix 8 in Supplement 1.

Secondary Outcomes on Efficacy and Effectiveness

Secondary analyses of the posttreatment ESs of IMI for depression showed a medium ES favoring IMI (g = −0.56; 95% CrI, −0.46 to −0.66). While the ES for human-guided IMI (g = −0.62, 95% CrI, −0.50

Table. Bayesian 3-Level Meta-Regression Results for HTE in Internet- and Mobile-Based Interventions for Depression[a]

Outcome	Studies, No.	Level 1 (95% CrI)	Level 2 (95% CrI)	Level 3 (95% CrI)
Primary outcome				
Posttreatment HTE	102	−0.02 (−0.07 to 0.03)	0.09 (0.05 to 0.13)	0.07 (0.01 to 0.12)
Subgroups analysis				
Study design characteristics				
Setting				
Effectiveness	24	−0.05 (−0.14 to 0.04)	0.04 (0.00 to 0.11)	0.10 (0.02 to 0.16)
Efficacy	78	0.00 (−0.07 to 0.07)	0.10 (0.06 to 0.14)	0.07 (0.01 to 0.13)
Control type				
Waiting list control	47	0.06 (−0.06 to 0.16)	0.13 (0.09 to 0.18)	0.06 (0.00 to 0.13)
TAU	27	−0.02 (−0.11 to 0.07)	0.05 (0.00 to 0.12)	0.09 (0.01 to 0.16)
Attention control	24	−0.05 (−0.14 to 0.04)	0.03 (0.00 to 0.10)	0.07 (0.01 to 0.14)
Intervention characteristics				
Guidance				
Guided	56	0.02 (−0.07 to 0.11)	0.10 (0.04 to 0.15)	0.08 (0.01 to 0.14)
Technical guidance	27	−0.07 (−0.16 to 0.02)	0.09 (0.02 to 0.15)	0.06 (0.00 to 0.13)
Unguided	25	−0.01 (−0.12 to 0.10)	0.05 (0.00 to 0.14)	0.11 (0.01 to 0.19)
Therapeutic background				
CBT	71	−0.01 (−0.08 to 0.05)	0.05 (0.00 to 0.10)	0.10 (0.03 to 0.14)
Third wave	14	−0.02 (−0.23 to 0.19)	0.06 (0.00 to 0.18)	0.10 (0.01 to 0.23)
Technology				
Internet-based	88	−0.03 (−0.08 to 0.03)	0.09 (0.05 to 0.13)	0.07 (0.01 to 0.12)
Other				
Publication period				
Last decade (≥2013)	82	−0.01 (−0.07 to 0.04)	0.10 (0.06 to 0.14)	0.07 (0.01 to 0.13)
Last 5 y (≥2018)	39	−0.03 (−0.13 to 0.06)	0.14 (0.09 to 0.19)	0.07 (0.00 to 0.16)
Post assessment time				
<6 mo	102	−0.00 (−0.05 to 0.04)	0.08 (0.06 to 0.11)	0.09 (0.05 to 0.12)
6 to 12 mo	21	−0.00 (−0.10 to 0.10)	0.03 (0.00 to 0.07)	0.03 (0.00 to 0.08)
≥1 y	16	−0.02 (−0.16 to 0.14)	0.03 (0.00 to 0.09)	0.06 (0.00 to 0.13
Moderation analysis				
Participant characteristics				
Age	94	0.01 (−0.02 to 0.04)	0.10 (0.06 to 0.14)	0.07 (0.01 to 0.12)
Percentage female	98	0.02 (−0.01 to 0.04)	0.09 (0.04 to 0.13)	0.07 (0.01 to 0.12)
Baseline severity	99	0.04 (0.01 to 0.07)	0.09 (0.04 to 0.12)	0.07 (0.01 to 0.11)
Other				
Assessment time		NA	0.08 (0.05 to 0.10)	0.08 (0.05 to 0.11)
Linear	102	−0.00 (−0.01 to 0.01)	NA	NA
Quadratic	102	−0.00 (−0.00 to 0.00)	NA	NA

Abbreviations: CBT, cognitive behavioral therapy; CrI, credible interval; HTE, heterogeneity of treatment effects; NA, not applicable; TAU, treatment as usual.

[a] Level 1 estimates in primary outcome and subgroup analysis quantify the HTE (logarithmic variance ratio $\hat{\mu}$; zero indicates equivalent variances in the intervention and control groups). Moderation analysis presents the association of the investigated variables with HTE ($\hat{\beta}$ zero indicates no effect on HTE). Level 2 estimates quantify how much estimates vary within studies. Level 3 estimates quantify the extent to which estimates vary between studies. 95% CrIs quantify the 95% interval in which the true estimate lies given the provided data. For extended results, including adjusting covariate estimate (lnER), see eAppendix 8 in Supplement 1.

to −0.75) compared with unguided IMI (g = −0.57, 95% CrI, −0.24 to −0.91) was higher, the difference was not significant overall (difference in gs, 0.07, 95% CrI, −0.17 to 0.31), in efficacy studies (difference in gs, 0.09, 95% CrI, −0.23 to 0.41), or in effectiveness studies (difference in gs, 0.01, 95% CrI, −0.25 to 0.27). From participant characteristics, only baseline severity was associated with the ES (β = −0.26, 95% CrI, −0.17 to −0.36). A significant interaction between guidance and baseline severity was found, suggesting the increased impact of therapeutic guidance with increasing baseline severity (interaction effect: β = −0.24, 95% CrI, −0.03 to −0.46). Detailed results on ES analyses can be found in eAppendix 9 in Supplement 1.

Discussion

To our knowledge, the present study is the first of its kind to systematically investigate the HTE in IMI for depression to evaluate to what extent patient-by-treatment interactions exist. There was a lack of evidence supporting meaningful variability in treatment effects across various settings and populations (lnVR = −0.02, 95% CrI, −0.07 to 0.03). However, meta-regression analysis revealed that baseline severity affected HTE ($\hat{\beta}$ = 0.04; 95% CrI, 0.01 to 0.07). Our findings indicate that patients with more severe depression responded differently to IMI and substantial patient-by-treatment interaction could be present in this subgroup. This supports that the average medium to large ES of IMI (g = −0.56; 95% CrI, −0.46 to −0.66) can be reasonably assumed for individuals with subthreshold to mild depression. In contrast, precision digital mental health care and future research are indicated for patients with moderate to severe depression to understand and counteract the increased HTE in that population.

Contrary to these findings for IMI, face-to-face psychotherapeutic approaches for depression show an overall HTE (lnVR = 0.09; 95% CrI, 0.06 to 0.14).[27] A key difference between IMI and face-to-face psychotherapy is the extent to which treatment protocols can be standardized and enforced.[145,146] While this might be a potential explanation for the difference in findings in face-to-face psychotherapy and the similarity to findings for other standardized treatment options (eg, antidepressants),[23,27] it is important to note that the present study design does not allow for causal interpretations. The finding regarding baseline severity and HTE does not mean that HTE is caused by the severity itself. Rather, it calls for future studies to investigate the causes of HTE in patients with mild to severe depression to pave the way toward precision digital depression treatment, where IMIs are only recommended to those patients with higher depression severity who are likely to benefit from IMI. Studies at the individual level, such as individual-patient data meta-analyses, could be promising to comprehend these diverse response patterns and their underlying causes.[147] Besides, our understanding of the mechanism of IMI is still limited, which makes it hard to explain why IMIs work.[31,148,149] More in-depth studies on the underlying mechanisms of change and effect analysis of specific components are highly needed to understand and optimize IMI for the treatment of depression.[31,148-151]

Regarding components of IMI, we found that human therapeutic guidance was associated with increased treatment effects from IMI in populations with higher depression severity (interaction effect: $\hat{\beta}$ = −0.24; 95% CrI, −0.03 to −0.46). Extending previous findings by Karyotaki and colleagues,[12] findings indicated no general superiority of guided interventions compared with unguided. Guidance did not provide an incremental benefit for subthreshold to mild depression; this difference was only found in higher levels of depression. This distinction may also explain the so-far inconsistent findings regarding the benefits of guidance.[11,12,31,32] Importantly, we did not find evidence for substantial HTE in the subset of guided IMIs, despite the involvement of human therapeutic elements (eg, personalized feedback and recommendations), which remove standardization to some extent. This option to personalize feedback and content to the patient may be a central reason why guidance was associated with the outcomes of IMI in higher severity.

For clinical practice, the key finding is that we replicated previous findings on the moderate to large ESs of IMIs throughout the efficacy and effectiveness analyses with an unprecedented sample

size of nearly 20 000 participants.[11,12] Especially the increase in effectiveness studies in recent years and the meta-analytically small to medium ES (g = −0.30; 95% CrI, −0.16 to −0.43) in studies conducted in pragmatic clinical settings[11] highlights the clinical value of IMIs beyond the laboratory. In conjunction with the results on the HTE and the associations of baseline severity and guidance, our findings suggest that unguided IMI can serve as standardized treatment for subthreshold to mild depression, showing clinically relevant meta-analytical effectiveness and no evidence for increased patient-by-treatment interactions (ie, clinically relevant mean differences but equivalent variances to active and passive control groups). In contrast, evidence for increased patient-by-treatment in moderate to severe depression indicates the need for a personalized precision approach for this population, for whom IMIs should only be used in yet-to-be-identified responding subgroups and human therapeutic guidance is involved (eg, to be able to react to the specific needs of individual patients). Similar to guidance, other dimensions to personalize IMIs to the individual (eg, content, order, or communication) might be able to reduce the HTE in this subgroup.[152] However, future RCTs investigating the effectiveness of these approaches are needed before robust recommendations can be made for patients with severe depression.

Limitations

When interpreting the present results, some limitations should be considered. First, we found within-study (level 2) and between-study (level 3) variances indicating differences between studies. To take these into account we used a 3-level bayesian meta-regression model and conducted sensitivity and subgroup analyses in more homogeneous studies, which replicated the core findings. However, level 2 and level 3 variances remained, and given the limited details provided in the included studies, we cannot rule out that operationalization of control types, implementation (eg, the extent or uptake of guidance), and settings differed between studies. Future studies should aim to reduce these variances by analyzing additional factors, such as differences between intervention components (eg, therapeutic content) or intervention design features (eg, persuasive design, engagement, aesthetics).[11,31,153-155]

Second, an aspect of particular importance for future studies is the type of technology used in IMIs. Most included studies were focused on internet-based interventions, allowing strong conclusions for this method of treatment delivery. However, other formats, such as smartphone- and app-based interventions, exist and are currently rising in the market.[11,14,154,156-159] The current body of evidence on the efficacy of mobile applications for depression is limited by the scarcity of high-quality RCTs, particularly in pragmatic clinical settings that use active control groups.[14,154,158,160] Moreover, due to the limited number of studies, reliable subgroup analyses were not feasible in this meta-analysis. As a result, caution should be exercised in generalizing the present findings of mainly internet-based interventions to app-based interventions or digital therapeutics in general.[11,14,150,154,157,158,161]

Third, given the limited sample variety, the generalizability of the present findings must be questioned. Except for 8 studies conducted in Asia, the vast majority of trials were conducted in Western industrialized countries, limiting the generalizability to other cultures and backgrounds.[162] Additionally, with roughly 70% of the participants being female, male participants and those with other genders are underrepresented in the current literature. As this is the first study of which we are aware investigating the HTE in IMIs, replications are needed to determine the generalizability of the findings, which is particularly true for these so-far-underrepresented samples in the field.

Additionally, although essential for evidence-based medicine and recommendations in treatment guidelines, meta-analyses on properly conducted RCTs remain exploratory. Hence, in particular, the here-found moderation results cannot replace the need for adequately designed confirmatory studies validating the findings of this study (eg, the superiority of guided IMI over unguided IMI in populations with higher severity levels). Furthermore, the present meta-analysis focused on depression severity and does not allow for generalization to other important outcomes, such as reliable improvement and deterioration, which require separate analysis in future studies.

Conclusions

In this systematic review and meta-analysis of the HTE of IMIs for depression, the equivalence in variance in IG and CG suggested that the average moderate treatment effect of IMI can be reasonably assumed for individuals with subthreshold to mild depression. However, HTE increased in individuals with moderate to high depression severity, indicating patient-by-treatment interaction and subgroups in this population particularly nonresponding. Future research on the causes of individual responses in this target group is required. Based on the current evidence, the use of unguided IMI for subthreshold to mild depression can be strongly recommended for clinical practice and policy as an effective, low-resource, time- and location-independent treatment. However, more studies are needed before the recommendation of IMIs can be generalized to populations with higher symptom burdens. Furthermore, human therapeutic guidance should be a central component moving forward to the treatment of individuals with more severe symptoms using IMIs.

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REFERENCES

1. Ettman CK, Abdalla SM, Cohen GH, Sampson L, Vivier PM, Galea S. Prevalence of depression symptoms in US adults before and during the COVID-19 pandemic. *JAMA Netw Open*. 2020;3(9):e2019686. doi:10.1001/jamanetworkopen.2020.19686

2. Santomauro DF, Mantilla Herrera AM, Shadid J, et al; COVID-19 Mental Disorders Collaborators. Global prevalence and burden of depressive and anxiety disorders in 204 countries and territories in 2020 due to the COVID-19 pandemic. *Lancet*. 2021;398(10312):1700-1712. doi:10.1016/S0140-6736(21)02143-7

3. James SL, Abate D, Abate KH, et al; GBD 2017 Disease and Injury Incidence and Prevalence Collaborators. Global, regional, and national incidence, prevalence, and years lived with disability for 354 diseases and injuries for 195 countries and territories, 1990-2017: a systematic analysis for the Global Burden of Disease Study 2017. *Lancet*. 2018;392(10159):1789-1858. doi:10.1016/S0140-6736(18)32279-7

4. Greenberg PE, Fournier AA, Sisitsky T, et al. The economic burden of adults with major depressive disorder in the United States (2010 and 2018). *Pharmacoeconomics*. 2021;39(6):653-665. doi:10.1007/s40273-021-01019-4

5. König H, König HH, Konnopka A. The excess costs of depression: a systematic review and meta-analysis. *Epidemiol Psychiatr Sci*. 2019;29:e30. doi:10.1017/S2045796019000180

6. Zhang Z, Jackson SL, Gillespie C, Merritt R, Yang Q. Depressive symptoms and mortality among US adults. *JAMA Netw Open*. 2023;6(10):e2337011. doi:10.1001/jamanetworkopen.2023.37011

7. Bobo WV, Grossardt BR, Virani S, St Sauver JL, Boyd CM, Rocca WA. Association of depression and anxiety with the accumulation of chronic conditions. *JAMA Netw Open*. 2022;5(5):e229817. doi:10.1001/jamanetworkopen.2022.9817

8. Cuijpers P, Noma H, Karyotaki E, Vinkers CH, Cipriani A, Furukawa TA. A network meta-analysis of the effects of psychotherapies, pharmacotherapies and their combination in the treatment of adult depression. *World Psychiatry*. 2020;19(1):92-107. doi:10.1002/wps.20701

9. Cuijpers P, Karyotaki E, Reijnders M, Ebert DD. Was Eysenck right after all? a reassessment of the effects of psychotherapy for adult depression. *Epidemiol Psychiatr Sci*. 2019;28(1):21-30. doi:10.1017/S2045796018000057

10. Cuijpers P, Harrer M, Miguel C, Ciharova M, Karyotaki E. Five decades of research on psychological treatments of depression: a historical and meta-analytic overview. *Am Psychol*. Published online November 16, 2023. doi:10.1037/amp0001250

11. Moshe I, Terhorst Y, Philippi P, et al. Digital interventions for the treatment of depression: a meta-analytic review. *Psychol Bull*. 2021;147(8):749-786. doi:10.1037/bul0000334

12. Karyotaki E, Efthimiou O, Miguel C, et al; Individual Patient Data Meta-Analyses for Depression (IPDMA-DE) Collaboration. Internet-based cognitive behavioral therapy for depression: a systematic review and individual patient data network meta-analysis. *JAMA Psychiatry*. 2021;78(4):361-371. doi:10.1001/jamapsychiatry.2020.4364

13. Andersson G. Internet-delivered psychological treatments. *Annu Rev Clin Psychol*. 2016;12(1):157-179. doi:10.1146/annurev-clinpsy-021815-093006

14. Firth J, Torous J, Nicholas J, et al. The efficacy of smartphone-based mental health interventions for depressive symptoms: a meta-analysis of randomized controlled trials. *World Psychiatry*. 2017;16(3):287-298. doi:10.1002/wps.20472

15. Ebert DD, Van Daele T, Nordgreen T, et al. Internet- and mobile-based psychological interventions: applications, efficacy, and potential for improving mental health. *Eur Psychol*. 2018;23(2):167-187. doi:10.1027/1016-9040/a000318

16. Lattie EG, Stiles-Shields C, Graham AK. An overview of and recommendations for more accessible digital mental health services. *Nat Rev Psychol*. 2022;1(2):87-100. doi:10.1038/s44159-021-00003-1

17. Andersson G, Hesser H, Veilord A, et al. Randomised controlled non-inferiority trial with 3-year follow-up of internet-delivered versus face-to-face group cognitive behavioural therapy for depression. *J Affect Disord*. 2013;151(3):986-994. doi:10.1016/j.jad.2013.08.022

18. Lappalainen P, Granlund A, Siltanen S, et al. ACT internet-based vs face-to-face? a randomized controlled trial of two ways to deliver acceptance and commitment therapy for depressive symptoms: an 18-month follow-up. *Behav Res Ther*. 2014;61:43-54. doi:10.1016/j.brat.2014.07.006

19. Selmi PM, Klein MH, Greist JH, Sorrell SP, Erdman HP. Computer-administered cognitive-behavioral therapy for depression. *Am J Psychiatry*. 1990;147(1):51-56. doi:10.1176/ajp.147.1.51

20. Kambeitz-Ilankovic L, Rzayeva U, Völkel L, et al. A systematic review of digital and face-to-face cognitive behavioral therapy for depression. *NPJ Digit Med*. 2022;5(1):144. doi:10.1038/s41746-022-00677-8

21. Reins JA, Buntrock C, Zimmermann J, 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*. 2021;90(2):94-106. doi:10.1159/000507819

22. Nakagawa S, Poulin R, Mengersen K, et al. Meta-analysis of variation: ecological and evolutionary applications and beyond. *Methods Ecol Evol*. 2015;6(2):143-152. doi:10.1111/2041-210X.12309

23. Volkmann C, Volkmann A, Müller CA. On the treatment effect heterogeneity of antidepressants in major depression: A Bayesian meta-analysis and simulation study. *PLoS One*. 2020;15(11):e0241497. doi:10.1371/journal.pone.0241497

24. Winkelbeiner S, Leucht S, Kane JM, Homan P. Evaluation of differences in individual treatment response in schizophrenia spectrum disorders: a meta-analysis. *JAMA Psychiatry*. 2019;76(10):1063-1073. doi:10.1001/jamapsychiatry.2019.1530

25. Brugger SP, Howes OD. Heterogeneity and homogeneity of regional brain structure in schizophrenia: a meta-analysis. *JAMA Psychiatry*. 2017;74(11):1104-1111. doi:10.1001/jamapsychiatry.2017.2663

26. Pillinger T, Osimo EF, Brugger S, Mondelli V, McCutcheon RA, Howes OD. A meta-analysis of immune parameters, variability, and assessment of modal distribution in psychosis and test of the immune subgroup hypothesis. *Schizophr Bull*. 2019;45(5):1120-1133. doi:10.1093/schbul/sby160

27. Kaiser T, Volkmann C, Volkmann A, Karyotaki E, Cuijpers P, Brakemeier EL. Heterogeneity of treatment effects in trials on psychotherapy of depression. *Clin Psychol Sci Pract*. 2022;29(3):294-303. doi:10.1037/cps0000079

28. Moggia D, Saxon D, Lutz W, Hardy GE, Barkham M. Applying precision methods to treatment selection for moderate/severe depression in person-centered experiential therapy or cognitive behavioral therapy. *Psychother Res*. Published online November 2, 2023. doi:10.1080/10503307.2023.2269297

29. Breedvelt JJF, Karyotaki E, Warren FC, et al. An individual participant data meta-analysis of psychological interventions for preventing depression relapse. *Nat Ment Health*. 2024;2(2):154-163. doi:10.1038/s44220-023-00178-x

30. Schwartz B, Cohen ZD, Rubel JA, Zimmermann D, Wittmann WW, Lutz W. Personalized treatment selection in routine care: integrating machine learning and statistical algorithms to recommend cognitive behavioral or psychodynamic therapy. *Psychother Res*. 2021;31(1):33-51. doi:10.1080/10503307.2020.1769219

31. Furukawa TA, Suganuma A, Ostinelli EG, et al. Dismantling, optimising, and personalising internet cognitive behavioural therapy for depression: a systematic review and component network meta-analysis using individual participant data. *Lancet Psychiatry*. 2021;8(6):500-511. doi:10.1016/S2215-0366(21)00077-8

32. Shim M, Mahaffey B, Bleidistel M, Gonzalez A. A scoping review of human-support factors in the context of Internet-based psychological interventions (IPIs) for depression and anxiety disorders. *Clin Psychol Rev*. 2017;57:129-140. doi:10.1016/j.cpr.2017.09.003

33. Heterogeneity of treatment effects in digital interventions for depression. OSF Registries. Accessed June 20, 2024. https://osf.io/cw3qp

34. Page MJ, McKenzie JE, Bossuyt PM, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. *BMJ*. 2021;372(71):n71. doi:10.1136/bmj.n71

35. Higgins JPT, Altman DG, Gøtzsche PC, et al; Cochrane Bias Methods Group; Cochrane Statistical Methods Group. The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. *BMJ*. 2011;343:d5928. doi:10.1136/bmj.d5928

36. Munder T, Barth J. Cochrane's risk of bias tool in the context of psychotherapy outcome research. *Psychother Res*. 2018;28(3):347-355. doi:10.1080/10503307.2017.1411628

37. Plöderl M, Hengartner MP. What are the chances for personalised treatment with antidepressants? detection of patient-by-treatment interaction with a variance ratio meta-analysis. *BMJ Open*. 2019;9(12):e034816. doi:10.1136/bmjopen-2019-034816

38. Stan Development Team. Stan. Accessed June 24, 2024. https://mc-stan.org/

39. Bürkner PC. brms: an R package for bayesian multilevel models using Stan. *J Stat Softw*. 2017;80(1):1-28. doi:10.18637/jss.v080.i01

40. Terhorst Y, Sander L, Brakemeier EL, Kaiser T. Heterogeneity of treatment effects in digital interventions for depression. OSF Home. Accessed June 20, 2024. https://osf.io/u3vdn/

41. Andersson G, Bergström J, Holländare F, Carlbring P, Kaldo V, Ekselius L. Internet-based self-help for depression: randomised controlled trial. *Br J Psychiatry*. 2005;187(5):456-461. doi:10.1192/bjp.187.5.456

42. Baumeister H, Paganini S, Sander LB, et al. Effectiveness of a guided internet- and mobile-based depression intervention for patients with chronic back pain and major depression (WARD-BP): a multicenter pragmatic randomized controlled trial. *Psychother Psychosom*. 2021;90(4):255-268.

43. Beevers CG, Pearson R, Hoffman JS, Foulser AA, Shumake J, Meyer B. Effectiveness of an internet intervention (Deprexis) for depression in a united states adult sample: A parallel-group pragmatic randomized controlled trial. *J Consult Clin Psychol*. 2017;85(4):367-380. doi:10.1037/ccp0000171

44. Beiwinkel T, Eißing T, Telle NT, Siegmund-Schultze E, Rössler W. Effectiveness of a web-based intervention in reducing depression and sickness absence: randomized controlled trial. *J Med Internet Res*. 2017;19(6):e213. doi:10.2196/jmir.6546

45. Berger T, Hämmerli K, Gubser N, Andersson G, Caspar F. Internet-based treatment of depression: a randomized controlled trial comparing guided with unguided self-help. *Cogn Behav Ther*. 2011;40(4):251-266. doi:10.1080/16506073.2011.616531

46. Birney AJ, Gunn R, Russell JK, Ary DV. MoodHacker mobile web app with email for adults to self-manage mild-to-moderate depression: randomized controlled trial. *JMIR Mhealth Uhealth*. 2016;4(1):e8. doi:10.2196/mhealth.4231

47. Boele FW, Klein M, Verdonck-de Leeuw IM, et al; Dutch Society for Neuro-Oncology (LWNO). Internet-based guided self-help for glioma patients with depressive symptoms: a randomized controlled trial. *J Neurooncol*. 2018;137(1):191-203. doi:10.1007/s11060-017-2712-5

48. Boeschoten RE, Dekker J, Uitdehaag BM, et al. Internet-based treatment for depression in multiple sclerosis: A randomized controlled trial. *Mult Scler*. 2017;23(8):1112-1122. doi:10.1177/1352458516671820

49. Braun L, Titzler I, Terhorst Y, et al. Are guided internet-based interventions for the indicated prevention of depression in green professions effective in the long run? Longitudinal analysis of the 6- and 12-month follow-up of a pragmatic randomized controlled trial (PROD-A). *Internet Interv*. 2021;26:100455. doi:10.1016/j.invent.2021.100455

50. Braun L, Titzler I, Terhorst Y, et al. Effectiveness of guided internet-based interventions in the indicated prevention of depression in green professions (PROD-A): Results of a pragmatic randomized controlled trial. *J Affect Disord*. 2021;278:658-671. doi:10.1016/j.jad.2020.09.066

51. Brog NA, Hegy JK, Berger T, Znoj H. Effects of an internet-based self-help intervention for psychological distress due to COVID-19: Results of a randomized controlled trial. *Internet Interv*. 2022;27:100492. doi:10.1016/j.invent.2021.100492

52. Buntrock C, Ebert D, Lehr D, et al. Effectiveness of a web-based cognitive behavioural intervention for subthreshold depression: pragmatic randomised controlled trial. *Psychother Psychosom*. 2015;84(6):348-358. doi:10.1159/000438673

53. Carlbring P, Hägglund M, Luthström A, et al. Internet-based behavioral activation and acceptance-based treatment for depression: a randomized controlled trial. *J Affect Disord*. 2013;148(2-3):331-337. doi:10.1016/j.jad.2012.12.020

54. Choi I, Zou J, Titov N, et al. Culturally attuned Internet treatment for depression amongst Chinese Australians: a randomised controlled trial. *J Affect Disord*. 2012;136(3):459-468. doi:10.1016/j.jad.2011.11.003

55. Christensen H, Griffiths KM, Jorm AF. Delivering interventions for depression by using the internet: randomised controlled trial. *BMJ*. 2004;328(7434):265. doi:10.1136/bmj.37945.566632.EE

56. Clarke G, Eubanks D, Reid E, et al. Overcoming Depression on the Internet (ODIN) (2): a randomized trial of a self-help depression skills program with reminders. *J Med Internet Res*. 2005;7(2):e16. doi:10.2196/jmir.7.2.e16

57. Clarke G, Kelleher C, Hornbrook M, Debar L, Dickerson J, Gullion C. Randomized effectiveness trial of an Internet, pure self-help, cognitive behavioral intervention for depressive symptoms in young adults. *Cogn Behav Ther*. 2009;38(4):222-234. doi:10.1080/16506070802675353

58. Clarke G, Reid E, Eubanks D, et al. Overcoming depression on the Internet (ODIN): a randomized controlled trial of an Internet depression skills intervention program. *J Med Internet Res*. 2002;4(3):E14. doi:10.2196/jmir.4.3.e14

59. de Graaf LE, Gerhards SAH, Arntz A, et al. Clinical effectiveness of online computerised cognitive-behavioural therapy without support for depression in primary care: randomised trial. *Br J Psychiatry*. 2009;195(1):73-80. doi:10.1192/bjp.bp.108.054429

60. de Graaf LE, Gerhards SAH, Arntz A, et al. One-year follow-up results of unsupported online computerized cognitive behavioural therapy for depression in primary care: A randomized trial. *J Behav Ther Exp Psychiatry*. 2011;42(1):89-95. doi:10.1016/j.jbtep.2010.07.003

61. Deady M, Mills KL, Teesson M, Kay-Lambkin F. An online intervention for co-occurring depression and problematic alcohol use in young people: primary outcomes from a randomized controlled trial. *J Med Internet Res*. 2016;18(3):e71. doi:10.2196/jmir.5178

62. Do R, Lee S, Kim JS, et al. Effectiveness and dissemination of computer-based cognitive behavioral therapy for depressed adolescents: Effective and accessible to whom? *J Affect Disord*. 2021;282:885-893. doi:10.1016/j.jad.2020.12.177

63. Ebert DD, Buntrock C, Lehr D, et al. Effectiveness of web- and mobile-based treatment of subthreshold depression with adherence-focused guidance: a single-blind randomized controlled trial. *Behav Ther*. 2018;49(1):71-83. doi:10.1016/j.beth.2017.05.004

64. Ebert DD, Lehr D, Boß L, et al. Efficacy of an internet-based problem-solving training for teachers: results of a randomized controlled trial. *Scand J Work Environ Health*. 2014;40(6):582-596. doi:10.5271/sjweh.3449

65. Ebert DD, Nobis S, Lehr D, et al. The 6-month effectiveness of Internet-based guided self-help for depression in adults with Type 1 and 2 diabetes mellitus. *Diabet Med*. 2017;34(1):99-107. doi:10.1111/dme.13173

66. Farrer L, Christensen H, Griffiths KM, Mackinnon A. Internet-based CBT for depression with and without telephone tracking in a national helpline: randomised controlled trial. *PLoS One*. 2011;6(11):e28099. doi:10.1371/journal.pone.0028099

67. Fischer A, Schröder J, Vettorazzi E, et al. An online programme to reduce depression in patients with multiple sclerosis: a randomised controlled trial. *Lancet Psychiatry*. 2015;2(3):217-223. doi:10.1016/S2215-0366(14)00049-2

68. Flygare AL, Engström I, Hasselgren M, et al. Internet-based CBT for patients with depressive disorders in primary and psychiatric care: Is it effective and does comorbidity affect outcome? *Internet Interv*. 2019;19:100303. doi:10.1016/j.invent.2019.100303

69. Forand NR, Barnett JG, Strunk DR, Hindiyeh MU, Feinberg JE, Keefe JR. Efficacy of guided iCBT for depression and mediation of change by cognitive skill acquisition. *Behav Ther*. 2018;49(2):295-307. doi:10.1016/j.beth.2017.04.004

70. Forsell E, Bendix M, Holländare F, et al. Internet delivered cognitive behavior therapy for antenatal depression: A randomised controlled trial. *J Affect Disord*. 2017;221:56-64. doi:10.1016/j.jad.2017.06.013

71. 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;16(7):e168. doi:10.2196/jmir.3539

72. 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;16(5):e121. doi:10.2196/jmir.3185

73. Gilbody S, Littlewood E, Hewitt C, et al; REEACT Team. Computerised cognitive behaviour therapy (cCBT) as treatment for depression in primary care (REEACT trial): large scale pragmatic randomised controlled trial. *BMJ*. 2015;351:h5627. doi:10.1136/bmj.h5627

74. Gladstone T, Terrizzi D, Stinson A, et al. Effect of internet-based cognitive behavioral humanistic and interpersonal training vs internet-based general health education on adolescent depression in primary care. *JAMA Netw Open*. 2018;1(7):e184278. doi:10.1001/jamanetworkopen.2018.4278

75. Gladstone T, Buchholz KR, Fitzgibbon M, Schiffer L, Lee M, Voorhees BWV. Randomized clinical trial of an internet-based adolescent depression prevention intervention in primary care: internalizing symptom outcomes. *Int J Environ Res Public Health*. 2020;17(21):7736. doi:10.3390/ijerph17217736

76. Glozier N, Christensen H, Naismith S, et al. Internet-delivered cognitive behavioural therapy for adults with mild to moderate depression and high cardiovascular disease risks: a randomised attention-controlled trial. *PLoS One*. 2013;8(3):e59139. doi:10.1371/journal.pone.0059139

77. Guo Y, Hong YA, Cai W, et al. Effect of a WeChat-based intervention (Run4Love) on depressive symptoms among people living with HIV in China: a randomized controlled trial. *J Med Internet Res*. 2020;22(2):e16715. doi:10.2196/16715

78. Hallford DJ, Austin DW, Takano K, Fuller-Tyszkiewicz M, Raes F. Computerized Memory Specificity Training (c-MeST) for major depression: A randomised controlled trial. *Behav Res Ther*. 2021;136:103783. doi:10.1016/j.brat.2020.103783

79. Hallgren M, Kraepelien M, Öjehagen A, et al. Physical exercise and internet-based cognitive-behavioural therapy in the treatment of depression: randomised controlled trial. *Br J Psychiatry*. 2015;207(3):227-234. doi:10.1192/bjp.bp.114.160101

80. Harrer M, Apolinário-Hagen J, Fritsche L, 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*. 2021;24:100374. doi:10.1016/j.invent.2021.100374

81. Ip P, Chim D, Chan KL, et al. Effectiveness of a culturally attuned Internet-based depression prevention program for Chinese adolescents: A randomized controlled trial. *Depress Anxiety*. 2016;33(12):1123-1131. doi:10.1002/da.22554

82. Johansson O, Bjärehed J, Andersson G, Carlbring P, Lundh LG. Effectiveness of guided internet-delivered cognitive behavior therapy for depression in routine psychiatry: A randomized controlled trial. *Internet Interv*. 2019;17:100247. doi:10.1016/j.invent.2019.100247

83. Johansson P, Westas M, Andersson G, et al. An internet-based cognitive behavioral therapy program adapted to patients with cardiovascular disease and depression: randomized controlled trial. *JMIR Ment Health*. 2019;6(10):e14648. doi:10.2196/14648

84. Johansson R, Ekbladh S, Hebert A, et al. Psychodynamic guided self-help for adult depression through the internet: a randomised controlled trial. *PLoS One*. 2012;7(5):e38021. doi:10.1371/journal.pone.0038021

85. Johansson R, Sjöberg E, Sjögren M, et al. Tailored vs. standardized internet-based cognitive behavior therapy for depression and comorbid symptoms: a randomized controlled trial. *PLoS One*. 2012;7(5):e36905. doi:10.1371/journal.pone.0036905

86. Kenter RMF, Cuijpers P, Beekman A, van Straten A. Effectiveness of a web-based guided self-help intervention for outpatients with a depressive disorder: short-term results from a randomized controlled trial. *J Med Internet Res*. 2016;18(3):e80. doi:10.2196/jmir.4861

87. Kivi M, Eriksson MCM, Hange D, et al. Internet-based therapy for mild to moderate depression in Swedish primary care: short term results from the PRIM-NET randomized controlled trial. *Cogn Behav Ther*. 2014;43(4):289-298. doi:10.1080/16506073.2014.921834

88. Krämer LV, Grünzig SD, Baumeister H, Ebert DD, Bengel J. Effectiveness of a guided web-based intervention to reduce depressive symptoms before outpatient psychotherapy: a pragmatic randomized controlled trial. *Psychother Psychosom*. 2021;90(4):233-242. doi:10.1159/000515625

89. Krämer R, Köhne-Volland L, Schumacher A, Köhler S. Efficacy of a web-based intervention for depressive disorders: three-arm randomized controlled trial comparing guided and unguided self-help with waitlist control. *JMIR Form Res*. 2022;6(4):e34330. doi:10.2196/34330

90. Lamers SMA, Bohlmeijer ET, Korte J, Westerhof GJ. The efficacy of life-review as online-guided self-help for adults: a randomized trial. *J Gerontol B Psychol Sci Soc Sci*. 2015;70(1):24-34. doi:10.1093/geronb/gbu030

91. Lappalainen P, Langrial S, Oinas-Kukkonen H, Tolvanen A, Lappalainen R. Web-based acceptance and commitment therapy for depressive symptoms with minimal support: a randomized controlled trial. *Behav Modif*. 2015;39(6):805-834. doi:10.1177/0145445515598142

92. Levin W, Campbell DR, McGovern KB, et al. A computer-assisted depression intervention in primary care. *Psychol Med*. 2011;41(7):1373-1383. doi:10.1017/S0033291710001935

93. Nygren T, Brohede D, Koshnaw K, Osman SS, Johansson R, Andersson G. Internet-based treatment of depressive symptoms in a Kurdish population: A randomized controlled trial. *J Clin Psychol*. 2019;75(6):985-998. doi:10.1002/jclp.22753

94. Liu H, Peng H, Song X, Xu C, Zhang M. Using AI chatbots to provide self-help depression interventions for university students: A randomized trial of effectiveness. *Internet Interv*. 2022;27:100495. doi:10.1016/j.invent.2022.100495

95. Löbner M, Pabst A, Stein J, et al. Computerized cognitive behavior therapy for patients with mild to moderately severe depression in primary care: A pragmatic cluster randomized controlled trial (@ktiv). *J Affect Disord*. 2018;238:317-326. doi:10.1016/j.jad.2018.06.008

96. Lokman S, Leone SS, Sommers-Spijkerman M, van der Poel A, Smit F, Boon B. Complaint-directed mini-interventions for depressive complaints: a randomized controlled trial of unguided web-based self-help interventions. *J Med Internet Res*. 2017;19(1):e4. doi:10.2196/jmir.6581

97. Lu SHX, Assudani HA, Kwek TRR, Ng SWH, Teoh TEL, Tan GCY. A randomised controlled trial of clinician-guided internet-based cognitive behavioural therapy for depressed patients in Singapore. *Front Psychol*. 2021;12:668384. doi:10.3389/fpsyg.2021.668384

98. Lukas CA, Eskofier B, Berking M. A gamified smartphone-based intervention for depression: randomized controlled pilot trial. *JMIR Ment Health*. 2021;8(7):e16643. doi:10.2196/16643

99. Meyer B, Bierbrodt J, Schröder J, et al. Effects of an internet intervention (Deprexis) on severe depression symptoms: randomized controlled trial. *Internet Interv*. 2015;2(1):48-59. doi:10.1016/j.invent.2014.12.003

100. Meyer B, Weiss M, Holtkamp M, et al. Effects of an epilepsy-specific Internet intervention (Emyna) on depression: Results of the ENCODE randomized controlled trial. *Epilepsia*. 2019;60(4):656-668. doi:10.1111/epi.14673

101. Milgrom J, Danaher BG, Gemmill AW, et al. Internet cognitive behavioral therapy for women with postnatal depression: a randomized controlled trial of MumMoodBooster. *J Med Internet Res*. 2016;18(3):e54. doi:10.2196/jmir.4993

102. Milgrom J, Danaher BG, Seeley JR, et al. Internet and face-to-face cognitive behavioral therapy for postnatal depression compared with treatment as usual: randomized controlled trial of MumMoodBooster. *J Med Internet Res*. 2021;23(12):e17185. doi:10.2196/17185

103. Mira A, Bretón-López J, García-Palacios A, Quero S, Baños RM, Botella C. An Internet-based program for depressive symptoms using human and automated support: a randomized controlled trial. *Neuropsychiatr Dis Treat*. 2017;13(101240304):987-1006. doi:10.2147/NDT.S130994

104. Montero-Marín J, Araya R, Pérez-Yus MC, et al. An Internet-based intervention for depression in primary care in Spain: a randomized controlled trial. *J Med Internet Res*. 2016;18(8):e231. doi:10.2196/jmir.5695

105. Moritz S, Schilling L, Hauschildt M, Schröder J, Treszl A. A randomized controlled trial of internet-based therapy in depression. *Behav Res Ther*. 2012;50(7-8):513-521. doi:10.1016/j.brat.2012.04.006

106. Nadort E, Schouten RW, Boeschoten RE, et al. Internet-based treatment for depressive symptoms in hemodialysis patients: A cluster randomized controlled trial. *Gen Hosp Psychiatry*. 2022;75:46-53. doi:10.1016/j.genhosppsych.2022.01.008

107. Newby J, Robins L, Wilhelm K, et al. Web-based cognitive behavior therapy for depression in people with diabetes mellitus: a randomized controlled trial. *J Med Internet Res*. 2017;19(5):e157. doi:10.2196/jmir.7274

108. Nobis S, Lehr D, Ebert DD, et al. Efficacy of a web-based intervention with mobile phone support in treating depressive symptoms in adults with type 1 and type 2 diabetes: a randomized controlled trial. *Diabetes Care*. 2015;38(5):776-783. doi:10.2337/dc14-1728

109. Noguchi R, Sekizawa Y, So M, Yamaguchi S, Shimizu E. Effects of five-minute internet-based cognitive behavioral therapy and simplified emotion-focused mindfulness on depressive symptoms: a randomized controlled trial. *BMC Psychiatry*. 2017;17(1):85. doi:10.1186/s12888-017-1248-8

110. O'moore KA, Newby JM, Andrews G, et al. Internet cognitive–behavioral therapy for depression in older adults with knee osteoarthritis: a randomized controlled trial. *Arthritis Care Res (Hoboken)*. 2018;70(1):61-70. doi:10.1002/acr.23257

111. Oehler C, Görges F, Rogalla M, Rummel-Kluge C, Hegerl U. Efficacy of a guided web-based self-management intervention for depression or dysthymia: randomized controlled trial with a 12-month follow-up using an active control condition. *J Med Internet Res*. 2020;22(7):e15361. doi:10.2196/15361

112. Perini S, Titov N, Andrews G. Clinician-assisted Internet-based treatment is effective for depression: randomized controlled trial. *Aust N Z J Psychiatry*. 2009;43(6):571-578. doi:10.1080/00048670902873722

113. Pfeiffer PN, Pope B, Houck M, et al. Effectiveness of peer-supported computer-based CBT for depression among veterans in primary care. *Psychiatr Serv*. 2020;71(3):256-262. doi:10.1176/appi.ps.201900283

114. Pots WTM, Fledderus M, Meulenbeek PAM, ten Klooster PM, Schreurs KMG, Bohlmeijer ET. Acceptance and commitment therapy as a web-based intervention for depressive symptoms: randomised controlled trial. *Br J Psychiatry*. 2016;208(1):69-77. doi:10.1192/bjp.bp.114.146068

115. Pugh NE, Hadjistavropoulos HD, Dirkse D. A randomised controlled trial of therapist-assisted, internet-delivered cognitive behavior therapy for women with maternal depression. *PLoS One*. 2016;11(3):e0149186. doi:10.1371/journal.pone.0149186

116. Raevuori A, Vahlberg T, Korhonen T, Hilgert O, Aittakumpu-Hyden R, Forman-Hoffman V. A therapist-guided smartphone app for major depression in young adults: a randomized clinical trial. *J Affect Disord*. 2021;286:228-238. doi:10.1016/j.jad.2021.02.007

117. Reins JA, Boß L, Lehr D, Berking M, Ebert DD. The more I got, the less I need? Efficacy of Internet-based guided self-help compared to online psychoeducation for major depressive disorder. *J Affect Disord*. 2019;246:695-705. doi:10.1016/j.jad.2018.12.065

118. Richards D, Timulak L, O'Brien E, et al. A randomized controlled trial of an internet-delivered treatment: its potential as a low-intensity community intervention for adults with symptoms of depression. *Behav Res Ther*. 2015;75:20-31. doi:10.1016/j.brat.2015.10.005

119. Ritvo P, Knyahnytska Y, Pirbaglou M, et al. Online mindfulness-based cognitive behavioral therapy intervention for youth with major depressive disorders: randomized controlled trial. *J Med Internet Res*. 2021;23(3):e24380. doi:10.2196/24380

120. Roepke AM, Jaffee SR, Riffle OM, McGonigal J, Broome R, Maxwell B. Randomized controlled trial of SuperBetter, a smartphone-based/internet-based self-help tool to reduce depressive symptoms. *Games Health J*. 2015;4(3):235-246. doi:10.1089/g4h.2014.0046

121. Rosso IM, Killgore WDS, Olson EA, et al. Internet-based cognitive behavior therapy for major depressive disorder: A randomized controlled trial. *Depress Anxiety*. 2017;34(3):236-245. doi:10.1002/da.22590

122. Ruwaard J, Schrieken B, Schrijver M, et al. Standardized web-based cognitive behavioural therapy of mild to moderate depression: a randomized controlled trial with a long-term follow-up. *Cogn Behav Ther*. 2009;38(4):206-221. doi:10.1080/16506070802408086

123. Salamanca-Sanabria A, Richards D, Timulak L, et al. A Culturally adapted cognitive behavioral internet-delivered intervention for depressive symptoms: randomized controlled trial. *JMIR Ment Health*. 2020;7(1):e13392. doi:10.2196/13392

124. Sander LB, Paganini S, Terhorst Y, et al. Effectiveness of a guided web-based self-help intervention to prevent depression in patients with persistent back pain. *JAMA Psychiatry*. 2020;77(10):1001-1011. doi:10.1001/jamapsychiatry.2020.1021

125. Schleider JL, Mullarkey MC, Fox KR, et al. A randomized trial of online single-session interventions for adolescent depression during COVID-19. *Nat Hum Behav*. 2022;6(2):258-268. doi:10.1038/s41562-021-01235-0

126. Schure MB, Lindow JC, Greist JH, et al. Use of a fully automated internet-based cognitive behavior therapy intervention in a community population of adults with depression symptoms: randomized controlled trial. *J Med Internet Res*. 2019;21(11):e14754. doi:10.2196/14754

127. Segal ZV, Dimidjian S, Beck A, et al. Outcomes of online mindfulness-based cognitive therapy for patients with residual depressive symptoms. *JAMA Psychiatry*. 2020;77(6):563-573. doi:10.1001/jamapsychiatry.2019.4693

128. Smith J, Newby JM, Burston N, et al. Help from home for depression: A randomised controlled trial comparing internet-delivered cognitive behaviour therapy with bibliotherapy for depression. *Internet Interv*. 2017;9:25-37. doi:10.1016/j.invent.2017.05.001

129. Smith P, Scott R, Eshkevari E, et al. Computerised CBT for depressed adolescents: Randomised controlled trial. *Behav Res Ther*. 2015;73:104-110. doi:10.1016/j.brat.2015.07.009

130. Spek V, Cuijpers P, Nyklícek I, et al. One-year follow-up results of a randomized controlled clinical trial on internet-based cognitive behavioural therapy for subthreshold depression in people over 50 years. *Psychol Med*. 2008;38(5):635-639. doi:10.1017/S0033291707002590

131. Spek V, Nyklícek I, Smits N, et al. Internet-based cognitive behavioural therapy for subthreshold depression in people over 50 years old: a randomized controlled clinical trial. *Psychol Med*. 2007;37(12):1797-1806. doi:10.1017/S0033291707000542

132. Sun Y, Li Y, Wang J, Chen Q, Bazzano AN, Cao F. Effectiveness of smartphone-based mindfulness training on maternal perinatal depression: randomized controlled trial. *J Med Internet Res*. 2021;23(1):e23410. doi:10.2196/23410

133. Titov N, Andrews G, Davies M, McIntyre K, Robinson E, Solley K. Internet treatment for depression: a randomized controlled trial comparing clinician vs. technician assistance. *PLoS One*. 2010;5(6):e10939. doi:10.1371/journal.pone.0010939

134. Titov N, Dear BF, Ali S, et al. Clinical and cost-effectiveness of therapist-guided internet-delivered cognitive behavior therapy for older adults with symptoms of depression: a randomized controlled trial. *Behav Ther*. 2015;46(2):193-205. doi:10.1016/j.beth.2014.09.008

135. Ünlü Ince B, Cuijpers P, van 't Hof E, van Ballegooijen W, Christensen H, Riper H. Internet-based, culturally sensitive, problem-solving therapy for Turkish migrants with depression: randomized controlled trial. *J Med Internet Res*. 2013;15(10):e227. doi:10.2196/jmir.2853

136. van Luenen S, Garnefski N, Spinhoven P, Kraaij V. Guided internet-based intervention for people with HIV and depressive symptoms: a randomised controlled trial in the Netherlands. *Lancet HIV*. 2018;5(9):e488-e497. doi:10.1016/S2352-3018(18)30133-4

137. Vernmark K, Lenndin J, Bjärehed J, et al. Internet administered guided self-help versus individualized e-mail therapy: A randomized trial of two versions of CBT for major depression. *Behav Res Ther*. 2010;48(5):368-376. doi:10.1016/j.brat.2010.01.005

138. Wagner B, Horn AB, Maercker A. Internet-based versus face-to-face cognitive-behavioral intervention for depression: a randomized controlled non-inferiority trial. *J Affect Disord*. 2014;152-154:113-121. doi:10.1016/j.jad.2013.06.032

139. Warmerdam L, van Straten A, Twisk J, Riper H, Cuijpers P. Internet-based treatment for adults with depressive symptoms: randomized controlled trial. *J Med Internet Res*. 2008;10(4):e44. doi:10.2196/jmir.1094

140. Williams AD, Blackwell SE, Mackenzie A, Holmes EA, Andrews G. Combining imagination and reason in the treatment of depression: a randomized controlled trial of internet-based cognitive-bias modification and internet-CBT for depression. *J Consult Clin Psychol*. 2013;81(5):793-799. doi:10.1037/a0033247

141. Wright B, Tindall L, Hargate R, Allgar V, Trépel D, Ali S. Computerised cognitive-behavioural therapy for depression in adolescents: 12-month outcomes of a UK randomised controlled trial pilot study. *BJPsych Open*. 2019;6(1):e5. doi:10.1192/bjo.2019.91

142. Wright B, Tindall L, Littlewood E, et al. Computerised cognitive-behavioural therapy for depression in adolescents: feasibility results and 4-month outcomes of a UK randomised controlled trial. *BMJ Open*. 2017;7(1):e012834. doi:10.1136/bmjopen-2016-012834

143. Young MD, Drew RJ, Kay-Lambkin F, et al. Impact of a self-guided, eHealth program targeting weight loss and depression in men: A randomized trial. *J Consult Clin Psychol*. 2021;89(8):682-694. doi:10.1037/ccp0000671

144. Zhao C, Wampold BE, Ren Z, Zhang L, Jiang G. The efficacy and optimal matching of an Internet-based acceptance and commitment therapy intervention for depressive symptoms among university students: A randomized controlled trial in China. *J Clin Psychol*. 2022;78(7):1354-1375. doi:10.1002/jclp.23329

145. Leichsenring F, Abbass A, Hilsenroth MJ, et al. Biases in research: risk factors for non-replicability in psychotherapy and pharmacotherapy research. *Psychol Med*. 2017;47(6):1000-1011. doi:10.1017/S003329171600324X

146. Kim DM, Wampold BE, Bolt DM. Therapist effects in psychotherapy: a random-effects modeling of the National Institute of Mental Health Treatment of Depression Collaborative Research Program data. *Psychotherp Res*. 2007;16(2):161-172. doi:10.1080/10503300500264911

147. Cuijpers P, Ciharova M, Quero S, et al. The contribution of "individual participant data" meta-analyses of psychotherapies for depression to the development of personalized treatments: a systematic review. *J Pers Med*. 2022;12(1):93. doi:10.3390/jpm12010093

148. Domhardt M, Steubl L, Boettcher J, et al. Mediators and mechanisms of change in internet- and mobile-based interventions for depression: a systematic review. *Clin Psychol Rev*. 2021;83:101953. doi:10.1016/j.cpr.2020.101953

149. Domhardt M, Grund S, Mayer A, et al. Unveiling mechanisms of change in digital interventions for depression: study protocol for a systematic review and individual participant data meta-analysis. *Front Psychiatry*. 2022;13:899115. doi:10.3389/fpsyt.2022.899115

150. Sakata M, Toyomoto R, Yoshida K, et al. Components of smartphone cognitive-behavioural therapy for subthreshold depression among 1093 university students: a factorial trial. *Evid Based Ment Health*. 2022;25(e1):e18-e25. doi:10.1136/ebmental-2022-300455

151. Watkins E, Newbold A, Tester-Jones M, Collins LM, Mostazir M. Investigation of active ingredients within internet-delivered cognitive behavioral therapy for depression: a randomized optimization trial. *JAMA Psychiatry*. 2023;80(9):942-951. doi:10.1001/jamapsychiatry.2023.1937

152. Hornstein S, Zantvoort K, Lueken U, Funk B, Hilbert K. Personalization strategies in digital mental health interventions: a systematic review and conceptual framework for depressive symptoms. *Front Digit Health*. 2023;5:1170002. doi:10.3389/fdgth.2023.1170002

153. Baumel A, Faber K, Mathur N, Kane JM, Muench F. Enlight: a comprehensive quality and therapeutic potential evaluation tool for mobile and web-based eHealth interventions. *J Med Internet Res*. 2017;19(3):e82. doi:10.2196/jmir.7270

154. Terhorst Y, Philippi P, Sander LB, et al. Validation of the mobile application rating scale (MARS). *PLoS One*. 2020;15(11):e0241480. doi:10.1371/journal.pone.0241480

155. Graham AK, Greene CJ, Kwasny MJ, et al. Coached mobile app platform for the treatment of depression and anxiety among primary care patients: a randomized clinical trial. *JAMA Psychiatry*. 2020;77(9):906-914. doi:10.1001/jamapsychiatry.2020.1011

156. Domhardt M, Messner EM, Eder AS, et al. Mobile-based interventions for common mental disorders in youth: a systematic evaluation of pediatric health apps. *Child Adolesc Psychiatry Ment Health*. 2021;15(1):49. doi:10.1186/s13034-021-00401-6

157. Torous J, Andersson G, Bertagnoli A, et al. Towards a consensus around standards for smartphone apps and digital mental health. *World Psychiatry*. 2019;18(1):97-98. doi:10.1002/wps.20592

158. Bae H, Shin H, Ji HG, Kwon JS, Kim H, Hur JW. App-based interventions for moderate to severe depression: a systematic review and meta-analysis. *JAMA Netw Open*. 2023;6(11):e2344120. doi:10.1001/jamanetworkopen.2023.44120

159. Huckvale K, Torous J, Larsen ME. Assessment of the data sharing and privacy practices of smartphone apps for depression and smoking cessation. *JAMA Netw Open*. 2019;2(4):e192542. doi:10.1001/jamanetworkopen.2019.2542

160. Terhorst Y, Rathner EM, Baumeister H, Sander LB. "Help from the app store?": a systematic review of depression apps in the German app stores. *Verhaltenstherapie*. 2018;28. doi:10.1159/000481692

161. Wang C, Lee C, Shin H. Digital therapeutics from bench to bedside. *NPJ Digit Med*. 2023;6(1):1-10. doi:10.1038/s41746-023-00777-z

162. Spanhel K, Balci S, Feldhahn F, Bengel J, Baumeister H, Sander LB. Cultural adaptation of internet- and mobile-based interventions for mental disorders: a systematic review. *NPJ Digit Med*. 2021;4(1):128. doi:10.1038/s41746-021-00498-1

SUPPLEMENT 1.

eAppendix 1. Illustration of Mean and Variance Differences in an RCT
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SUPPLEMENT 2.

eTable. Study Characteristics

SUPPLEMENT 3.

Data Sharing Statement