Psychiatria Danubina, 2022; Vol. 34, Suppl. 8, pp 155-163 *Conference paper*

THE EFFICACY OF MOBILE PHONE-BASED INTERVENTIONS FOR THE TREATMENT OF DEPRESSION: A SYSTEMATIC META-REVIEW OF META-ANALYSES OF RANDOMIZED CONTROLLED TRIALS

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SUMMARY

Background: *Depression is ranked by the World Health Organization as the single largest contributor to global disability. The shortage of health care resources, conditions of social distancing during the present pandemic, and the continuing need of patients with subclinical depression and in remission for supportive therapies, all together motivate a search for new approaches to deliver appropriate and timeous treatment for depression.*

Subjects and methods: *We conducted a systematic literature search of meta-analyses and systematic reviews on the topic of mobile apps for the treatment of depression using the Medline (Pubmed) database during the period ending March 30th, 2022. This review was managed following the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) guidelines and entailed a search strategy using key-words related to depressive states and mobile phone apps for depression treatment and management.*

Results: *A total of 15 full-text articles met the inclusion criteria for the current systematic review. 13 of the 15 studies reported on the effectiveness of mobile apps for treating depression, finding a significant reduction in depressive symptoms with small-to-medium positive effect size. Patients with severe depression experienced greater benefits from a behavioral activation app, whereas those with mild depression responded better to a mindfulness app. The impact of clinicians' support is difficult to isolated completely from the particular interventions' effects.*

Conclusions: *Mobile-based intervention apps present a convenient tool for prevention and supportive therapy of depression. The use of mobile apps may act as an efficient intervention to reduce depression in adult patients regardless the potential contributing factors of gender or co-morbidities, but the role of mobile apps should be contrasted with other digital interventions.*

Key words: *depression – mobile-based interventions – mobile apps – mental health – mHealth - smartphone applications – digital psychiatry*

Abbreviations: *CBT - Cognitive behavioral therapy; CI - confidence interval; PICO-SD - P: participants, I: intervention, C: comparison, O: outcome, and SD: study design; PRISMA - Preferred Reporting Items for Systematic Review and Meta-Analysis; SD - Standard deviation; SE - Standard error*

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INTRODUCTION

Depression is a common illness worldwide, with an overall prevalence of approximately 3.8%, including 5.0% among adults and 5.7% among adults older than 60 years (Institute of Health Metrics and Evaluation 2021). Severe depression is a major risk factor for suicide, which is the fourth leading cause of death in 15-29-year-olds (Institute of Health Metrics and Evaluation 2021). The worldwide prevalence of clinical depression increased 2.5-fold during the COVID-19 pandemic and related lockdown measures (Fountoulakis et al. 2022). Suicidality rates have also increased accordingly in many countries, including Greece (Fountoulakis et al. 2021b), Hungary (Kulig et al. 2020), Latvia (Vrublevska et al. 2021), Romania (Panfil et al. 2022), and Russia (Syunyakov et al. 2022). Nonetheless, access to mental health care remains insufficient, as almost half of the world's population lives in countries with less than one psychiatrist per 100,000 people (World Health Organization 2015). The shortage of health care resources and the continuing needs of patients with subclinical depression and in remission for supportive therapies make it necessary to find new cost-effective methods and approaches to deliver treatment to suffering patients (Batra et al. 2017).

Goldberg et al. defined mobile phone-based interventions as behavioral interventions that are delivered remotely through mobile phones. This can include a wide variety of approaches such as smartphone apps, text message-based interventions, apps integrated with wearable sensors, as well as interventions that combine

a mobile phone component with additional support (Goldberg et al. 2022). The first meta-review of meta-analyses by Lecomte et al. reported medium effect sizes for interventions using mobile apps, but with evidence that was generally of poor to moderate quality (Lecomte et al. 2020). When considering apps focusing on depressive symptoms, Lecomte et al. found small effect sizes compared with active controls such as an experimental treatment or a previously approved treatment with known effectiveness, with overall good-quality evidence, especially for more recent meta-analyses. On the other hand, recent meta-review by Goldberg et al. failed to find convincing evidence in support of any mobile phone-based intervention on any outcomes, which extended from depression, anxiety, and stress to text message interventions on smoking cessation.

These results suggest that mobile phone-based interventions may hold only modest promise for reducing common psychological symptoms such as depression and anxiety, although with generally small effect sizes, and a failure to outperform conventional therapeutic interventions, i.e., specific active controls. Despite the modest effect sizes, the relatively low cost and high scalability of most of app-based interventions tested supports their importance for public health (Goldberg et al. 2022).

In the present study we aimed to examine the efficacy of treatment mobile-based apps for depression in adults based on findings of previous meta-analyses and a systematic review of the literature on evidence-based studies.

SUBJECTS AND METHODS

Search strategy

We conducted a systematic literature search in Medline (Pubmed) for the period ending on March 30th, 2022. This review was conducted in accordance with the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) guidelines (Moher et al. 2009). We used the following search terms formula: ("meta-analysis" OR "systematic review") AND depression AND ("smartphone*" OR "smart phone" OR "mobile phone" OR "mobile app*" OR "mobile device" OR "mobile-based" OR "mobile health" OR "mhealth" OR "m-health").

Selection criteria

The research question was based on PICO-SD (P: participants, I: intervention, C: comparison, O: outcome, and SD: study design) developed by the Cochrane Collaboration (Higgins et al. 2011). The first author reviewed the searched articles based on the following eligibility criteria: Inclusion criteria were the following: (i) The study assessed smartphone applications; (ii) The smartphone application targeted depression in an adult clinical or subclinical population; (iii) One main outcome measure was symptoms of depression; (iv) The study was written in English language; (v) The study was a systematic review or a meta-analysis. Exclusion criteria were: (i) The app was not used for treatment of depression; (ii) The population included only adolescents, children, pregnant women, or older people; (iii) The app did not target depression; (iv) Outcomes did not reflect symptoms of depression, (v) The study was not written in English language; (vi) The study was not a systematic review or meta-analysis.

Data extraction

The first author (DA) extracted the key data on the characteristics of the studies including authorship, publication year, type of study, number of included studies, relevant primary outcome measure, main findings, and the quality assessment.

Quality assessment

The quality of each study included in this review was assessed using the six basic criteria of the Cochrane Risk of Bias Assessment Tool (Higgins et al. 2011). This consists of screening for biases such as (i) random sequence generation, (ii) allocation concealment, (iii) blinding criteria, (iv) incomplete outcome data, (v) selective reporting, (vi) and other biases.

Meta-analysis

To perform a meta-analysis DA extracted individual studies from reference lists of systematic reviews. The following inclusion criteria were used for eligible studies: 1) information was provided on either pre- post information of group sizes, depression score means and standard deviations (SD) or standard errors (SE), or within-group mean (SD or SE) differences; 2) Interventions utilized a mobile app interface to provide any psychosocial modality in a structured manner other than self-monitoring or self-help; 3) Inactive control group, no intervention, or provision of general information; 4) Depression severity measurement using valid scales that provide continuous or ordinal data; 5) Comparable background depression severity between intervention and inactive control groups, as the primary/secondary outcome; 6) Study duration exceed the time-frame of analysis by the depression assessment tool; 7) Study aimed to assess acute rather than maintenance efficacy; 8) Adult population (age ≥ 18). Study eligibility was assessed and reviewed by TS (80%) and DA (20%). Dubious cases were discussed by the team together under supervision of DS. Quality assessment was performed with respect to the quality of random allocation, blinding, sample size calculation, and primary or secondary endpoints.

Within-group changes of depression scores were calculated. using GraphPad Prism Software, while meta-analysis was performed using SPSS 28.0 Software (Cohen's d, corresponding 95% confidence interval limits and p-values). We performed Random-effect meta-analysis using the REML estimation method. Heterogeneity was assessed using I^2-heterogeneity test. Publication bias effect were assessed via funnel plot symmetry evaluation, with subsequent analysis of sensitivity of results to exclusion of outliers. Also, we performed subgroup analysis by a study population type, intervention modality, primary goal of a study, and primary/secondary depression evaluation.

RESULTS

Selection and inclusion of studies

Of the 200 abstracts initially identified, 154 papers were excluded from the review based on their irrelevance to the topic according to review of the abstract's content. Another 31 articles were eliminated from the remaining 46 full-text articles after an assessment of eligibility criteria through reading the full text articles. The main reasons for these exclusions were as follows: (1) study participants did not match the inclusion criteria (n=4); (2) mobile and internet interventions had been assessed together simultaneously (n=3); (3) no information on efficacy was presented (n=24). Finally, a total of 15 full-text articles accurately met all the inclusion criteria for the current preplanned systematic review. Figure 1 depicts a flow diagram detailing the review process and results at each stage of the literature search.

Characteristics of included studies

Study characteristics are shown in Table 1. Studies included an average of 25.5 studies (SD = 21.4, range = 8 to 83). Average meta-analysis quality was 6.7 out of 8 (SD = 1.0, range = 4 to 8). 10 studies out of 15 received a score of 7 or 8, indicating a "good" quality of the assessment. Studies were published during the period between 2013 and 2022 with an average sample size of 3817 (SD = 3918.0, range = 227 to 15,530).

Risk of bias within the studies

Most studies evaluated the risk of bias (k=13, 87.0%), most commonly using the Cochrane tool (k=12, 80.0%). One study used both the Cochrane tool and GRADE, one study used GRADE and Jadad, and the other study used both Cochrane tool and their own scales. Blinding of personnel and participants was the area most consistently rated as bringing a high risk for bias (56.0%), and other biases was the second most common factor (31.3%). Random sequence generation and selective reporting was rated as low (72.5 and 72.9%).

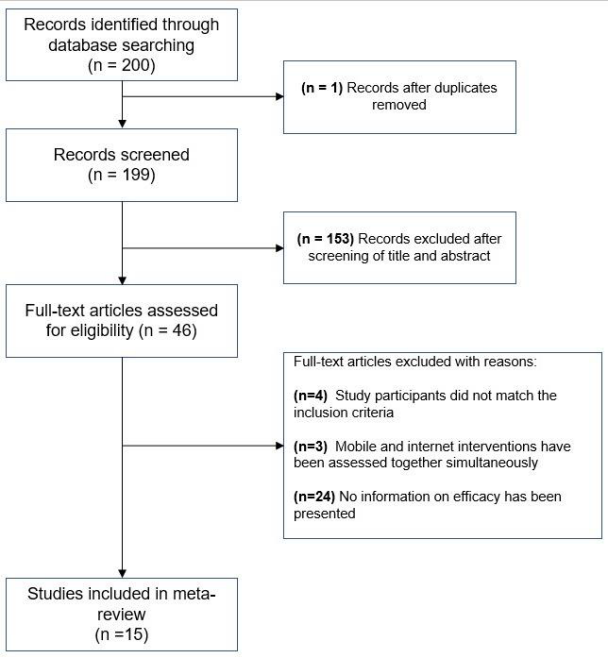

Figure 1. PRISMA flow chart for the study selection of meta-analyses on the use of mobile phone apps for depression treatment

Meta-analysis

After extraction of individual studies and removing the duplicates, a total of 42 pairs of Intervention-Control comparisons from 36 studies fulfilled eligibility criteria for the meta-analysis, with a duration that ranged from three weeks to three months. Among these, 14 studies were conducted on students or workers without a diagnosed mental health condition and without cut-off score depression score as an inclusion criterion, ten studies were conducted on patients with diagnosed mental disorder, seven on patients with somatic disorder and 11 on a general population with clearly defined higher levels of depression scores. Only one pair was double-blind and four were single-blinded. All studies but one used randomization, though 13 comparisons utilized randomization methods that could potentially be a source of bias (simple, sequential, envelope, or not properly defined methods). In 23 comparisons, depression score changes were a primary outcome. The Forest plot of all studies and subgroup analysis can be seen in Figure 2 which clearly shows a net positive effect of the interventions. The cumulative effect size (Cohen's d [CI 95%]) for all comparison pairs (n=42) was d=0.185 [0.097; 0.273] ($p<0.001$). Heterogeneity analysis showed a high level of heterogeneity ($Tau^2=0.04$, $H^2=2.15$, $I^2=54.1\%$). On the basis of subgroup analysis, effect sizes were larger in otherwise healthy participants (n=14, pooled Cohen's d = 0.257 [0.142; 0.373], $I^2=0.6\%$) and participants with somatic disorders (n=7, 0.345 [0.151; 0.540], $I^2 = 0\%$), both $p<0.001$. Effect sizes were lower in studies that involved either a clinical population (n=10, 0.071 [-0.093; 0.236], $p=0.397$, $I^2 = 41.0\%$) or in

Table 1. Characteristics of included meta-analysis studies on the use of mobile phone apps for depression treatment

References	Type of study	Number of included studies and participants	Relevant primary outcome measure	Main findings	NIH	Quality assessment
Batra et al. (2017)	Systematic review	18 studies, 1000 participants	n/a	• two studies demonstrated the efficacy of delivering psychotherapy via mobile apps • where evaluated, good correlation between mobile assessment scores and standard clinical assessments was observed, supporting the clinical applicability of the apps	5	n/a
Donker et al. (2013)	Systematic review	3 studies	PHQ-9, BDI-II	• the mobile-type app was the only intervention that failed to yield any significant direct effect on depression • repeated self-monitoring over time using ecological momentary assessment on a mobile device may increase emotional self-awareness and thereby reduce depressive symptoms	6	Cochrane
Firth et al. (2017)	Meta-analysis	18 studies, 3414 participants	PHQ-9, MADRS, DASS, HAM-D, CES-D, BDI-II, PHQ-8, HADS	• small-to-moderate positive effect size of smartphone mental health interventions for reducing depressive symptoms in comparison to control conditions • the effects of smartphone interventions which were delivered entirely via the smartphone device appeared larger • Subgroup analyses found that the effects of smartphone interventions were substantially larger when compared to inactive than active control conditions • significant benefits of smartphone apps were only found for those with self-reported mild-to-moderate depression • neither age nor gender had any relationship with the study effect size	8	Cochrane
Gál et al. (2021)	Meta-analysis	15 studies	n/a	• significant small or medium size effects of mindfulness apps compared to control conditions for symptoms of depression • studies using waitlist controls resulted in slightly higher effect sizes across all outcomes	7	Cochrane
Hennemann et al. (2018)	Systematic review	16 studies, 4680 participants	PHQ-9, HADS-T, BDI, BDI-II	• study results on relapse and rehospitalization rates were inconsistent, including reduced risk ratios for recurrent depression	7	Cochrane, GRADE
Hrynyschyn & Dockweiler (2021)	Systematic Review	8 studies, 1534 participants	CES-D, BDI-II, PHQ-8,9, DAS	• all studies investigated the effects on depression symptoms; however, the reported results of these studies are inconsistent • no evident results could be found for smartphone-based CBT among patients with depression • the studies which compared a smartphone-based therapy app with a waitlist control group revealed significant differences	7	Cochrane, two scales dealing with study designs and study performance
Kerst et al. (2019)	Systematic review	12 studies, 1247 participants	PHQ, BDI	• app-based interventions lead to a reduction of symptoms of depression in all reviewed studies • clinician support makes it difficult to completely isolate the intervention effects • the effects of the interventions may be smaller compared to active controls than to inactive control groups	4	n/a
Kim et al. (2022)	Meta-analysis	14 studies, 1307 participants	DASS, BDI-II, MADRS, HAM-D, HDRS 17, PANSS, CDS	• the pooled mobile app interventions showed statistically significant and positive effects for reducing the disease-related symptoms • the findings of this study identified the advantages of apps that included features for individualized feedback and reminder notifications • the findings indicated that the use of additional strategies, such as phone calls or emails as a part of the intervention was more effective than app-alone interventions • the incorporation of CBT-based strategies was predominant	8	Cochrane
Linardon et al. (2019)	Meta-analysis	54 studies	n/a	• app-supported smartphone interventions significantly outperformed control conditions in improving depressive symptoms • the statistically significant effect sizes were observed in both symptomatic and non-symptomatic • studies that offered professional guidance and engagement reminders were consistently associated with larger effect sizes • CBT vs. non-CBT-based smartphone interventions reported no differences in level of symptom improvement • smartphone interventions did not significantly differ from active interventions on any outcome	7	Cochrane

Table 1. Continues

References	Type of study	Number of included studies and participants	Relevant primary outcome measure	Main findings	NIH	Quality assessment
Moshe et al. (2021)	Meta-analysis	83 studies, 15530 participants	PHQ-9, CES-D	• a medium pooled effect size superiority of digital interventions across all control conditions with benefits sustained at follow-up • three studies that directly compared digital interventions with face-to-face therapy found no significant difference • larger effect sizes in interventions with a human support component • effect sizes were significantly lower for effectiveness studies than in efficacy trials • no significant difference in outcomes between males and females • no difference in the effectiveness of digital interventions in patients with comorbid somatic conditions compared with those without • greater effect size for participants with higher pretreatment depression severity than those with lower baseline symptom scores	8	Cochrane
Planas & Yuguero (2021)	Systematic review	22 studies, 3858 participants	PHQ-2,8,9, BDI-II, DASS-21, BDI	• in most of the selected studies, the symptoms related to depression were reduced at the end of the proposed intervention, and some reported benefits in the follow-up period, weeks or months later • considering whether the results they achieve are due to the content they offer or simply due to using them. This has been called "digital placebo"	6	GRADE, Jadad
Rathbone & Prescott (2017)	Systematic Review	27 studies, 4658 participants	PHQ-9, DASS, BDI-II	• the app has provided promising indication of their efficacy to improve a patient's physical and mental health state • the majority of all participants ranked the usability and feasibility of, and satisfaction with, their allocated mHealth intervention as satisfactory to high	5	Cochrane
Serrano-Ripoll et al. (2022)	Meta-analysis	12 trials, 2859 participants	PHQ-9, PHQ-8 BDI-II, DASS-21, CES-D	• 71% (10/14) of the interventions led to a significant reduction in depressive symptoms • the interventions led to better results in trials focusing on moderate to severe depression symptomatology	8	Cochrane
Versluis et al. (2016)	Meta-analysis	33 studies, 882 participants	BDI PHQ-8, POMS, GIDS-c, MADRS, DASS, Valence 2-items GSI BSI Depression 3-items	• the effect on mental health was 62% larger when the EMI was part of a treatment package that included support of a mental health professional compared with stand-alone EMI. • both the within- and the between-subject analyses indicate that mobile technologies can be effectively used to deliver interventions for mental health. • the finding that the effect of EMIs was stronger when support by a mental health professional was included is in line with findings from research on Internet interventions. • no moderation effects were found for the other study or intervention characteristics • equally effective for healthy versus clinical individuals	8	Cochrane
Weisel et al. (2019)	Meta-analysis	6 studies, 796 participants	PHQ-8,9, DASS, CES-D, BDI-II	• significant pooled effects were found for depression, with small effect sizes and moderate heterogeneity • the accumulating evidence for digital mental health interventions delivered through the internet as an effective mean to treat mental health disorders cannot be directly translated to digital interventions delivered via standalone mobile apps	7	Cochrane

Note: BDI-II - Beck Depression Inventory-II; BSI - Brief Symptom Inventory; CBT - Cognitive behavioral therapy; CDS - Calgary Depression Scale; CES-D - Center for Epidemiologic Studies Depression; DASS - Depression Anxiety Stress Scale; EMI - Ecological Momentary Interventions; GIDS-c - Quick Inventory of Depressive Symptoms-Clinician rated; GSI - General Symptom Index; HADS - Hospital Anxiety and Depression Scale; HAM-D, HDRS - Hamilton Rating Scale for Depression, Montgomery–Åsberg Depression Rating Scale; n\a - not applicable; NIH = National Institutes of Health Quality Assessment of Systematic Reviews and Meta-Analyses Tool; PANSS - Positive and Negative Syndrome Scale; PHQ-8, PHQ-9 - Patient Health Questionnaire-8, -9: POMS - Profile of Mood States

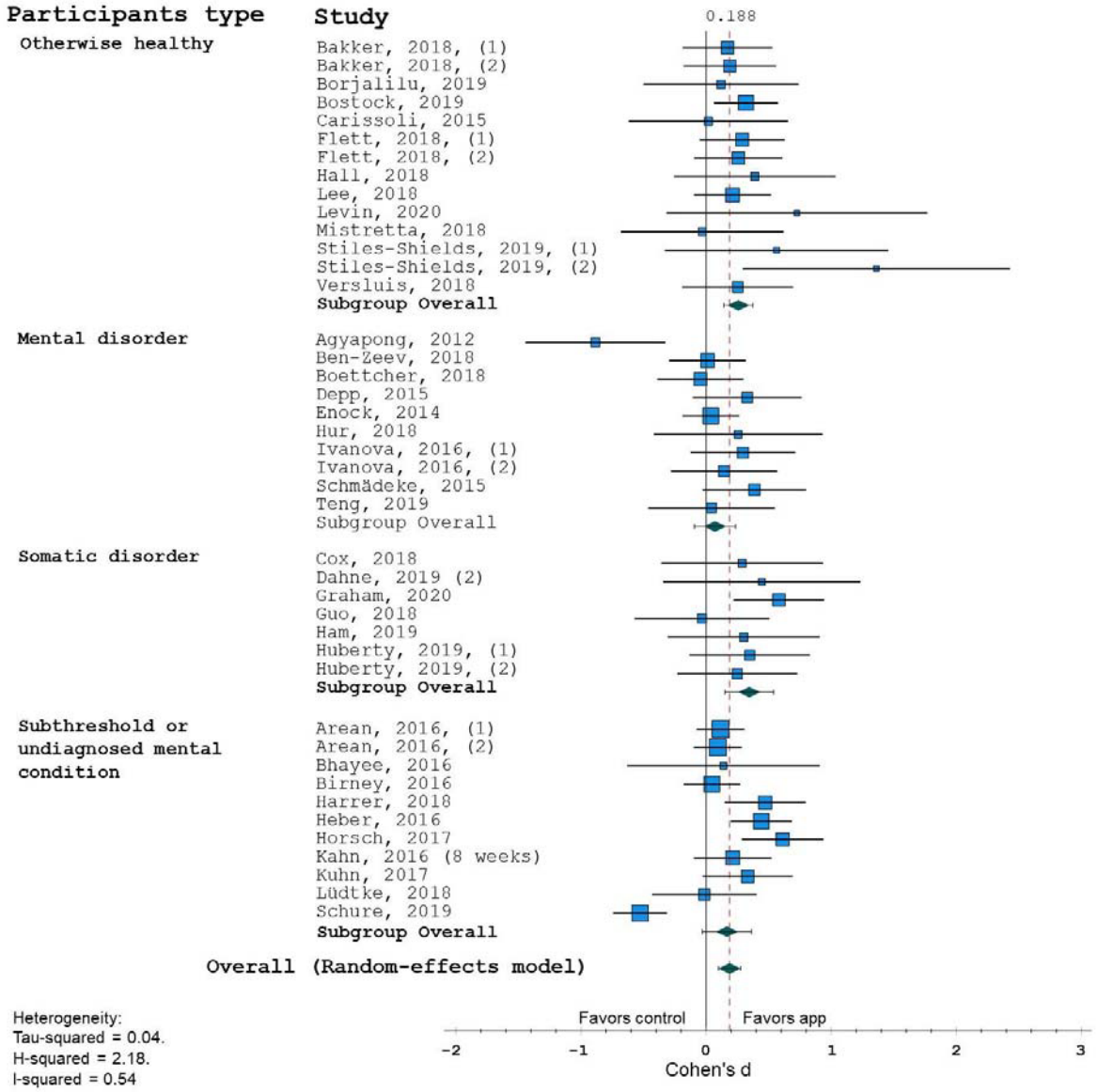

Figure 2. Forest plot of meta-analysis results with subgroups according to the type of participants in studies on the use of mobile phone apps for depression treatment

studies with clearly defined lower limits of depression severity scores on a corresponding psychometric tool (n=11, 0.167 [-0.029; 0.363], p=0.096, I^2=81.5%). Subgroups of studies with inclusion of patients with confirmed depressive episodes showed no difference relative to the control (n=3, d=0.000 [-0.89; 0.88, p=0.99]). Among intervention types, significant (p<0.001) effect size was reported for apps with a complex treatment approach (n=9, 0.285 [0.141; 0.428]) and for mindfulness apps (n=15, 0.276 [0.161; 0.391]), while the remaining options were either not distinguishable from control (Acceptance and commitment therapy (n=2), CBT (n=13), Cognitive control (n=3)) or worse than control (supportive text messaging: n=1, -0.885 [-1.445; -0.325], p=0.002). The Funnel plot (Figure 3) showed asymmetry of meta-analysis results and seven outlier studies that can indicate a publication bias favoring the obtained positive results. Indeed, trim-and-fill analysis with imputation of 14 missed studies to fulfill funnel-plot symmetry resulted in decreased pooled effect size (n=56, 0.072 [-0.017; 0.161, p=0.113]). Sensitivity analysis showed that exclusion of outlier studies did not significantly affect the overall results.

DISCUSSION

13 out of 15 studies meeting all the criteria reported the effectiveness of mobile apps for treating depression and significant reduction in depressive symptoms due to their use with small-to-medium positive effect size (Weisel et al. 2019). The results of our meta-analysis show negligible overall effects of mobile app interventions comparing to inactive control in reducing depressive symptoms (effect size d<0.2). Although the studies

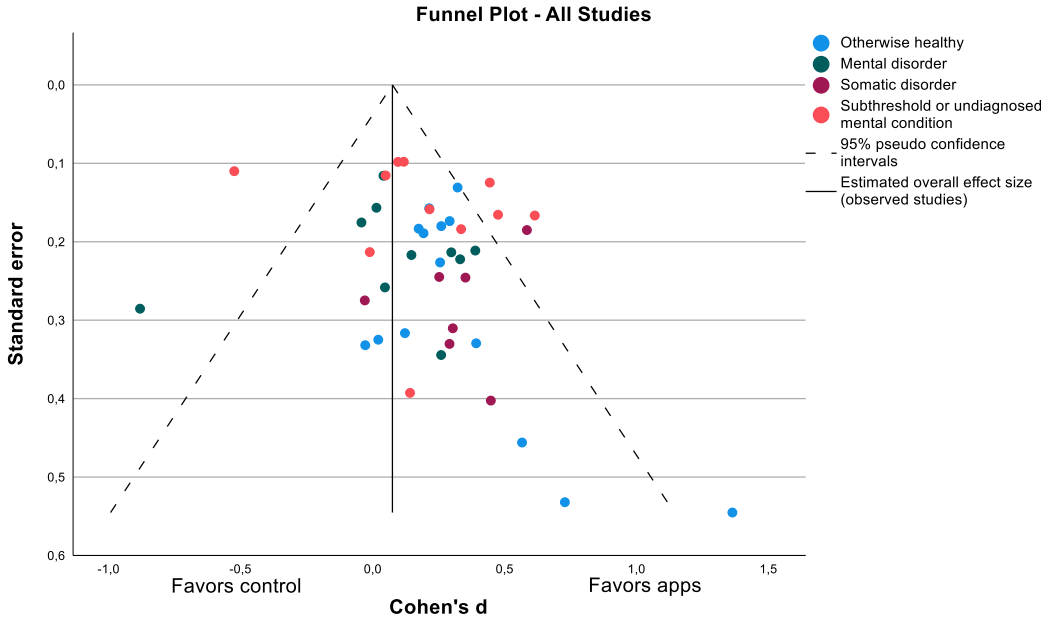

Figure 3. Funnel plot of meta-analysis results with subgroups according to the type of participants in studies on the use of mobile phone apps for depression treatment

showed high heterogeneity, this was attributable to studies conducting with mixed populations of clinically relevant psychiatric conditions and subthreshold depression. Subgroup analysis results suggest that in these two populations, the effect sizes were indistinguishable from that in the corresponding control groups. This may be due to add-on treatment with mobile apps having a significantly lesser contribution that was obtained by conventional medical treatment with antidepressants. Otherwise, the absence of effect of mobile apps in these studies might be attributable to significantly disturbed cognitive functioning that precluded fruitful or consistent use of self-administered smartphone apps. Nevertheless, mobile apps showed promising effect in otherwise mentally healthy populations under stressful conditions with low (Cohen's d from 0.2 to 0.5) but significant pooled effect sizes emerging in those studies.

Patients have noted the usability, feasibility, and their satisfaction with mobile-based interventions for depression (Rathbone & Prescott 2017). Advantages of certain apps also included features for individualized feedback and reminder notifications (Kim et al. 2022).

Our results are in disagreement with other studies showing a larger effect for interventions that targeted patients with more severe depression (Moshe et al. 2021, Serrano-Ripoll et al. 2022). However, significant benefits of smartphone apps were only found for those with self-reported mild-to-moderate depression (Firth et al. 2017). As for duration of therapeutic responses, effects were maintained at follow-up for anxiety symptoms, stress and quality of life, but not for depressive symptoms (Gal et al. 2021), or were reduced at the end of the proposed intervention, while some studies reported persistence of benefits in the follow-up period (Planas & Yuguero 2021). Other evidence likewise indicated that benefits were sustained at follow-up (Moshe et al. 2021).

Neither gender nor age had any influence on the outcomes (Firth et al. 2017, Moshe et al. 2021). Statistically significant effect sizes were observed in both clinical and subthreshold samples (Linardon et al. 2019, Versluis et al. 2016). Moreover, there were no differences in the effectiveness of digital interventions in depressive patients with comorbid somatic conditions compared with those without comorbidity (Moshe et al. 2021). Studies that offered professional guidance were generally associated with larger effect sizes (Linardon et al. 2019, Moshe et al. 2021). As for choice of methods, there was a predominant incorporation of CBT-based strategies (Hrynyschyn & Dockweiler 2021, Kim et al. 2022). Patients with more severe depression experienced greater benefits from the behavioral activation app, whereas those with mild depression benefitted more from the mindfulness app (Firth et al. 2017). It was difficult to isolate completely clinician support from primary intervention effects (Kerst et al. 2019).

CONCLUSIONS

Prevention and supportive therapy for depression require new approaches that can exploit a remotely administered format and long-term follow-up. Mobile device-based interventions are user-friendly, feasible, and satisfying methods that can maintain user engagement along with high compliance, and at low cost. The use of mobile apps is effective in adult patients with depression regardless of gender and comorbidities.

However, the effect size of treatments delivered by mobile app may range from negligible to low, depending on the participant's clinical subgroup. However, the additional support of a healthcare professional is an important component for ensuring the effectiveness of this kind of therapy. The predominant technique used in mobile apps is CBT, but mindfulness meditation is also reported. The use of mobile apps in depression therapy, as compared to other digital interventions such as internet interventions and text messaging, needs to be further explored.

Limitations of the study

First, we note that our study relies on results of previous reviews, and therefore may propagate their weaknesses. Nevertheless, we extracted from those reviews unique study data and conducted an independent meta-analysis. Our major limitation lies in that most of the published studies were conducted on populations without any diagnosed mental health condition, such that our results may not be reliably generalized. Most of the studies encountered selection and attrition biases that possibly could have affected their results.

Acknowledgements: *None.*

Conflict of interest: *None to declare.*

Contribution of individual authors:

Darya Astafeva & Daria Smirnova formulated the primary idea, elaborated the research hypothesis, and fixed the keywords search algorithm.

Darya Astafeva & Timur Syunyakov designed the study, searched and reviewed literature, extracted data from the studies, wrote the first draft of the manuscript.

Timur Syunyakov analyzed the data targeting meta-review approach.

Timur Syunyakov & Daria Smirnova share senior authorship of this manuscript.

Al authors contributed to the detailed revision, as well as approved the final version of the article for its submission.

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