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Digital Interventions for the Treatment of Depression: A Meta-Analytic Review

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The high global prevalence of depression, together with the recent acceleration of remote care owing to the COVID-19 pandemic, has prompted increased interest in the efficacy of digital interventions for the treatment of depression. We provide a summary of the latest evidence base for digital interventions in the treatment of depression based on the largest study sample to date. A systematic literature search identified 83 studies (N = 15,530) that randomly allocated participants to a digital intervention for depression versus an active or inactive control condition. Overall heterogeneity was very high (I^2 = 84%). Using a random-effects multilevel metaregression model, we found a significant medium overall effect size of digital interventions compared with all control conditions (g = .52). Subgroup analyses revealed significant differences between interventions and different control conditions (WLC: g = .70; attention: g = .36; TAU: g = .31), significantly higher effect sizes in interventions that involved human therapeutic guidance (g = .63) compared with self-help interventions (g = .34), and significantly lower effect sizes for effectiveness trials (g = .30) compared with efficacy trials (g = .59). We found no significant difference in outcomes between smartphone-based apps and computer- and Internet-based interventions and no significant difference between human-guided digital interventions and face-to-face psychotherapy for depression, although the number of studies in both comparisons was low. Findings from the current meta-analysis provide evidence for the efficacy and effectiveness of digital interventions for the treatment of depression for a variety of populations. However, reported effect sizes may be exaggerated because of publication bias, and compliance with digital interventions outside of highly controlled settings remains a significant challenge.

Public Significance Statement

This meta-analysis demonstrates the efficacy of digital interventions in the treatment of depression for a variety of populations. Additionally, it highlights that digital interventions may have a valuable role to play in routine care, most notably when accompanied by human guidance. However, compliance with digital interventions remains a major challenge, with little more than 50% of participants completing the full intervention on average.

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Depression is one of the leading causes of disability worldwide, estimated to affect more than 300 million people globally each year (World Health Organization, 2017). Depression has been identified as a risk factor for many chronic health conditions (Krishnan et al., 2002), is associated with poor quality of life (Saarni et al., 2007), and has a significant burden of fatal and nonfatal disease (Jia et al., 2015) and substantial societal and economic costs (Greenberg & Birnbaum, 2005).

It is well established that psychotherapy is effective in the treatment of depression for a variety of populations and across a number of settings (Barth et al., 2013; Cuijpers, Karyotaki, et al., 2020; Cuijpers, Quero, Dowrick, et al., 2019; Zhou et al., 2015). Psychotherapy has been proven to be as effective as antidepressants for patients with mild to moderate depression (Campbell et al., 2013; Cuijpers, Noma, et al., 2020) and is the preferred first line of treatment for depression for the majority of patients (McHugh et al., 2013; McManus et al., 2016). Psychotherapy may also be more effective than medication in the longer term (Karyotaki et al., 2016). However, despite the demonstrated efficacy, many people remain untreated (Herrman et al., 2019; James et al., 2018). The ability to access psychotherapy is a major challenge in most countries. Barriers include the low availability of trained health care providers, high treatment costs, and stigma (Patel et al., 2011; Saraceno et al., 2007; World Health Organization, 2011).

The coronavirus pandemic 2019 (COVID-19) has exacerbated these challenges further. Early evidence suggests that a "parallel mental health curve" may be developing, as the incidence of mental health conditions, including depression, has risen significantly since the start of the pandemic (Jacobson et al., 2020; Kola et al., 2021; Pan et al., 2021; Pierce et al., 2020). Moreover, as governments across the world deploy widespread measures intended to reduce the incidence of the virus—including restrictions on individual movement and social interaction—many clinicians and patients are no longer able to meet face-to-face, prompting an urgent need for researchers and clinicians to find novel methods of delivering evidence-based mental health care. Digital interventions have been proposed as a viable solution to meet this need (Torous, Myrick, et al., 2020). With more than 59% of the global population now able to access to the Internet (Worldwide Digital Population as of April 2020, n.d.), digital interventions may offer highly scalable solutions for the delivery of evidence-based treatments without the need for meeting in-person.

In addition to improving access to health care, digital interventions may also help answer the question of what makes psychotherapy work. Unlike in face-to-face therapy, where treatment may vary and therapists may "drift" away from the treatment protocol (Waller, 2009), the highly standardized nature of digital interventions allows for the manipulation of individual mediators while controlling for others. With the ability to capture detailed data related to every event (e.g., the therapeutic content delivered, participant interactions, and proximal outcomes), digital interventions may provide researchers with a new experimental paradigm to better understand the mechanisms of change in psychotherapy (Domhardt et al., 2019; Domhardt, Steubl, et al., 2021; Holmes et al., 2018). Such data can then be analyzed to inform treatment development and delivery that may also provide valuable insights for the amelioration of face-to-face therapy itself (Bateup et al., 2020; Domhardt, Cuijpers, et al., 2021). Furthermore, the ability to include large sample sizes with relatively little effort enables researchers to conduct sufficiently powered trials to detect the small effect sizes likely in studies on individual components and mediators of change (Cuijpers, Cristea, et al., 2019; Domhardt, Steubl, et al., 2021).

Finally, because digital interventions are well-positioned to leverage the latest advances in technology such as smartphones, wearable devices, and artificial intelligence (Baumeister & Montag, 2019; Fulmer et al., 2018; Mohr, Zhang, et al., 2017), they may also accelerate the development of treatment formats targeted at the individual. For example, smartphone-delivered ecological momentary assessment (where an individual reports on their behaviors, cognitions, and symptoms in real-time in their natural environment), and digital phenotyping approaches (where digital traces of individuals' daily life are passively tracked) may be used to generate personalized models of psychopathology by providing data related to individual symptom networks and how the relationship between symptoms evolve over time at the intraindividual level (Insel, 2017; McNally, 2016; Montag et al., 2020; Robinaugh et al., 2020; Wichers, 2014). Such information can then be used to tailor interventions toward specific symptoms that hold the greatest importance in the network, thereby allowing us to move closer to the promise of precision medicine in psychotherapy (Blanken et al., 2020; Firth et al., 2017; Nahum-Shani et al., 2018).

What Are Digital Interventions?

Emerging in the late 1980s (Ghosh et al., 1988), the first versions of digital interventions were little more than a therapeutic manual delivered on a computer via a CD-ROM (Selmi et al., 1990). With the development and widespread adoption of the Internet in the 1990s, interventions have evolved considerably to embrace the latest developments in technology (Andersson, 2016; Andersson et al., 2019), with smartphone-delivered interventions now becoming one of the most popular methods of accessing care (Linardon et al., 2019; Weisel et al., 2019).

Although formats vary considerably, digital interventions typically require patients to login to a software program, website, or app to read, watch, listen to, and interact with content structured as a series of modules or lessons (Andersson, 2018; Ebert et al., 2018). Individuals often receive homework assignments relating to the modules and regularly complete digitally-administered questionnaires relevant to their presenting problems, allowing clinicians to monitor their progress and outcomes in cases in which digital interventions comprise human support (Andersson et al., 2009; Singla et al., 2018).

Digital interventions may offer a number of potential advantages over traditional face-to-face therapy. First, the ability for patients to access interventions at any time and from anywhere with an Internet connection significantly lowers the barrier to access (Ebert et al., 2018). Second, the relative anonymity of digital interventions might lower the stigma around receiving professional treatment for depression. Third, the time savings associated with digital interventions may enable health care providers to increase the delivery of therapy and reduce wait-list times, making it a highly scalable and potentially more cost-effective form of therapy (Hedman et al., 2012; Kraepelien et al., 2018; Paganini et al., 2018; Richards et al., 2020; Singla et al., 2018; Titov et al., 2018; Titov, Dear, Staples, Bennett-Levy, et al., 2015).

Over the past 30 years, digital interventions have been developed and tested for a range of mental disorders, the most common of which are anxiety and depression disorders (Andersson et al., 2019; Ebert et al., 2018; Königbauer et al., 2017). Interventions have employed a variety of therapeutic approaches—from cognitive behavioral therapy (CBT; Andersson, 2009) to acceptance and commitment therapy (ACT; Brown et al., 2016), psychodynamic approaches (Johansson et al., 2013), and interpersonal psychotherapy (Donker, Bennett, et al., 2013). Digital interventions have also been investigated in the treatment of people with depressive symptoms and comorbid somatic conditions (Bendig et al., 2018), including diabetes (Ebert et al., 2017; Newby et al., 2017; Nobis et al., 2015), musculoskeletal diseases (Baumeister et al., 2021; O'Moore et al., 2018; Sander, Paganini et al., 2020), and epilepsy (Meyer et al., 2019). As depression and (chronic) somatic conditions frequently co-occur—leading to substantial adverse effects for patients, including poor treatment compliance, increased symptom burden, additional medical complications and higher treatment costs (Barnett et al., 2012; Goldberg, 2010)—digital interventions may provide an adjunctive psychotherapeutic measure to address the interdependency of physical and mental conditions and improve the continuity of care in cases where specially trained health care practitioners may not be readily available (Fineberg, 2012; Shrank et al., 2019; Singla et al., 2018).

The Efficacy of Digital Interventions

Hundreds of randomized controlled trials (RCTs) and a growing number of effectiveness studies (Andersson & Hedman, 2013; Hedman et al., 2014; Johansson, Bjärehed, et al., 2019; Titov, Dear, Staples, Bennett-Levy, et al., 2015) and meta-analyses have been published demonstrating the efficacy of digital interventions for various mental disorders (Andersson & Cuijpers, 2009; Cuijpers et al., 2013; Cuijpers, Andersson, et al., 2011; Karyotaki et al., 2017; 2018; Königbauer et al., 2017; Spek et al., 2007). Meta-analyses on digital interventions for depression have reported pooled standardized mean differences (SMDs) ranging from .32 (Spek et al., 2007) to .90 (Königbauer et al., 2017) for interventions compared with placebo, treatment as usual, and wait-list control, with benefits maintained at both 3–6 months (g = .15) and 9–18 months follow-up (g = .22; Andrews et al., 2018; see Table 1 for a summary of prior meta-analyses on digital interventions for depression).

A particularly important comparison for digital interventions is with face-to-face therapy. Although theoretical models of psychotherapy have proposed that a face-to-face therapist is required for large treatment effects (Wampold, 2001)—and, indeed, many practitioners hold the same belief (Topooco et al., 2017)—recent research suggests that there may be no significant difference in outcomes between the two treatment formats (Cuijpers, Noma, et al., 2020). A meta-analysis by Carlbring et al. (2018) comparing Internet-based CBT with face-to-face therapy for depression demonstrated that there was no significant difference in the average effect sizes between the two formats when digital interventions are accompanied by some form of remote human guidance. However, the aforementioned meta-analysis may have been limited by several sources of heterogeneity as studies targeting a wide range of mental disorders across all control types and including both individual face-to-face and group-based therapy were pooled together. Furthermore, sample sizes of many of the included studies may have been too small to detect differences in comparative or noninferiority trials. Another challenge in establishing noninferiority is that the interventions themselves are often substantially different. Digital interventions are typically brief, structured interventions with a limited set of treatment components, whereas face-to-face therapy is often significantly broader in scope, containing a wider variety of specific and nonspecific therapeutic factors. Given the substantial difference in amount of therapist time required to deliver face-to-face therapy compared with digital interventions (7.8 times the amount, according to the meta-analysis by Andrews et al. (2018) and the ability for digital interventions to scale the delivery of care outside of in-person settings, robust studies establishing noninferiority thus have major clinical and practical implications on meeting the treatment gap in mental health care.

Another important consideration regarding digital interventions is the efficacy of smartphone-based applications (apps). Over the past decade the number of smartphone apps available for download has proliferated, with a recent count identifying more than 10,000 apps for mental health alone (Torous et al., 2018). Smartphone apps may offer a number of advantages over computer- and Internet-based interventions, including the ability to monitor symptoms in real-time and in situ as well as providing automated notifications for fostering greater intervention adherence. At the same time, smartphone sensors may be used to facilitate the collection of additional data sources related to the individual and their environment (e.g., GPS data related to movement, physical activity and sleep; Mohr, Zhang, et al., 2017; Moshe et al., 2021). Yet, despite their growing availability and potential, a number of concerns have been raised over the lack of evidence-base supporting these apps (Larsen et al., 2019). A review of smartphone apps for mental health by Weisel and colleagues (2019) revealed only 19 published RCTs covering a heterogenous set of several mental disorders (depression, anxiety, substance use, self-injurious thoughts and behaviors, PTSD, and sleep problems) and only one study with an overall low risk of bias. Only one trial in the meta-analysis demonstrated the efficacy of an app-based intervention for depression as the primary outcome, but the trial was affected by an attrition rate of 74% at posttest (Roepke et al., 2015). A meta-analytic review by Firth et al. (2017) identified 18 RCTs for depression and found that smartphone apps led to a greater reduction in depressive symptoms (g = .38) when compared with a combination of active control conditions (including attentional control conditions, in-person interventions, other forms of patient contact and pharmacotherapy) and inactive control conditions (where participants received no intervention during the trial period or were put

Table 1
Prior Systematic Reviews and Meta-Analyses on Digital Interventions for Depressive Symptoms

Meta-analyses	Primary outcome	Target population[a]	*M* Age (*SD*); Range	Comparison/Control conditions	Intervention Delivery mode	Theoretical orientation	*N* Included RCTs	*N* PPTs	Effect size [95 % CI]	Heterogeneity I^2	Search date
Andersson & Cuijpers, 2009	Depression	Adults (18+), MDD via diagnostic Interview or elevated levels of depressive symptoms based on self—report measures	—	TAU, WLC, Other	Internet-based or computerized treatment	CBT, Other	12	2,446	Overall: $d = 0.41$ [0.29–0.54]	57.49	from 1966 to January 2009
Andrews et al., 2018	Symptom severity	Adults (18+), MDD, Panic Disorder with/ without Agoraphobia, Social Anxiety Disorder, Generalized Anxiety Disorder	—	WLC, IC, TAU, placebo	Computerized and Internet-based	CBT	All = 53 Studies, 64 Trials; MDD = 32	All = 8,279 MDD = 5,642	Overall: $g = 0.80$ [0.68–0.92] MDD: $g = 0.67$ [0.51–0.81]	Overall: 84 MDD: 84	September 2016
Andrews et al., 2000	Anxiety and depressive Disorders	Adults (Major Depression, Panic Disorder, Social Phobia, Generalized Anxiety Disorder)	—	WLC (+discussion group), IC, TAU, Self-monitoring control	Computerized and Internet-based	CBT	All = 22 Studies; MDD = 6	—	Overall $g = 0.88$ [0.76–0.99]MDD: $g = 0.78$ [0.59–0.96]	Overall: 7.84 MDD: 0	January 2009 to Dec 2009
Carlbring et al., 2018		Adults MDD/Other	—	Face-to facePsychotherapy (single/group)	ICBT	CBT	20	1,418	MDD: $g = -.02$ [−.22–.19]	Overall: 42 MDD: N/A	June 2013
Cuijpers, Andersson, et al., 2011	Depressive disorder	Adults MDD	—	WLC; TAU; pill placebo; psychologicalplacebo); 2) pharmacotherapy, psychological and pharmacological treatment;individual psychologicalvs group treatment	Computerized/ internet-based	Several (BAT, PST, IPT, psychoeducation)	12	2,446	$d = 0.41$ [0.29 –0.54]	NA	January 2010
Cuijpers, Andersson, Donker, et al., 2011	MDD symptoms	Adults MDD		TAU (4 studies), WLC (2 studies), Contact with GP (1 study)	Internet-based, Bibliotherapy	CBT, Other	7	1,362	$d = 0.28$ [0.14,0.42]	28.73	January 2010
Ebert et al., 2015	Depression and anxiety symptoms	Children/adolescents up to 25 years	—	WLC (10 studies), placebo (3 studies)	Computerized and Internet- based	CBT	13	796	Overall: $g = 0.72$ [0.55−0.90]	20.14	December 2013
Firth et al., 2017	Primary depression, comorbid depression, subclinical depressive symptoms	Adults/depressive symptoms	18−59	WLC, active, antidepressant medication	Smartphone-based/ computerized	CBT, several	18	3,414	Overall: $g = 0.38$ [0.24−0.52]	74	May 2017
Garrido et al., 2019	Depression and anxiety	Children/adolescents 12−25 years	—	WLC, active control (online materials), psycho-educational content	DMHI (Digital Mental Health Interventions)	CBT, others	15	3,294	DMHI vs no-intervention: $d = 0.33$ [0.11-0,55], DMHI vs active control: $d = 0.14$ [−0.04−0.31]	70	

(*table continues*)

Table 1 (*continued*)

Meta-analyses	Primary outcome	Target population[a]	*M* Age (*SD*); Range	Comparison/Control conditions	Intervention Delivery mode	Theoretical orientation	*N* Included RCTs	*N* PPTs	Effect size [95 % CI]	Heterogeneity I^2	Search date
Karyotaki et al., 2017	self-report scale of depression/ Depressive Symptoms Severity	Adults /depressive symptoms	Mean = 42	TAU, WLC or attention control	Internet-based	CBT	16	3,876	Traditional Meta-analysis $g = 0.33$; [0.19−0.46] IPDMA $g = 0.27$ [CI, 0.17−0.37]	71	January 2016
Karyotaki, Ebert, et al., 2018 guided	Acute depression	Adults/depressive symptoms	Mean = 42.5	WLC, TAU, web-based discussion groups, web-based psychoeducation	Internet-based	CBT, PST	24 studies	4,889	one-stage IPDMA OR (response) of 2.49 [2.17−2.85] NNT = 4.74 [4.21−5.46], one-stage IPDMA OR (remission) of 2.41[2.07–2.79] NNT = 5.98, [4.35–6.80] two-stage IPDMA OR (response) of 2.76 [2.23−3.41] NNT = 4.16 [3.41−5.26],Two-stage IPDMA OR (remission) of 2.80 [2.21–3.56] NNT = 5.26 [4.34−6.66]	Two-stage (response): 58 Two-stage (remission): 54%	January 2016
Karyotaki, Ebert, et al., 2018 unguided	Symptoms of depression	Adults/depressive symptoms	IG: 41.37, CG: 42.49	WLC, TAU, attention placebo or other nonactive control conditions	Internet based	CBT	13	3,805	one-stage IPDMA OR = 0.62 [0.46–0.83] Two-stage IPDMA 0.62 [0.48–0.81]	Two-stage: 0	January 2016
Königbauer et al., 2017	symptom severity of depression	Adults diagnosed depression; major depression and/or persistentdepressive disorder/dysthymia	41.4	IMI, WLC, App, Attention control, group CBT, online discussion group, no treatment	Internet-/mobile-based	CBT	19	1,650	IMI vs WL $g = -0.90$ [95% −1.07, −0.73], IMI vs APP $g = -0.17$[−0.49-0.15] IMI vs IMI g = range from −0.64 to −2.24	092	June 2016
Linardon et al., 2019	MDD others	Adults	—	WLC, active control (attention/placebo-based) group	app-supported smartphone interventions	CBT, others (mostly acceptance- or mindfulness-based principles)		—	0.28 [0.21−0.36]	54	May 2017
Richards and Richardson, 2012	depression	Adults	—	WLC, TAU, Other	Internet-based	CBT, PST, structured writing intervention	19	2,996	$d = .56$ [−.71, −.41]	81	March 2001–March 2011
Spek et al., 2007	Symptoms of depression	>18, adults	—	TAU, Attention placebo, online discussion, psychoeducation, self-monitoring, WLC, therapist assisted therapy	internet based	CBT	12	2,334	$g = 0.27$ [0.15–0.40]	70.1	1990 to February 2006

(*table continues*)

Table 1 (*continued*)

Meta-analyses	Primary outcome	Target population[a]	*M* Age (*SD*); Range	Comparison/Control conditions	Intervention Delivery mode	Theoretical orientation	*N* Included RCTs	*N* PPTs	Effect size [95 % CI]	Heterogeneity I^2	Search date
Weisel et al., 2019	MDD, others	>18, adults	—	no-treatmentcontrol conditions, WLC, informationonly, sham group, daily mood chart.	smartphone apps	CBT, PST, Mindfulness, others	Overall: 19, MDD primary target: 6	Overall: 3,681 MDD Primary target: 796	MDD Primary target g = 0.33 [0.10–0.57]	MDD: 59	February 2018
Wells et al., 2018	Symptoms of depression	>16	—	No treatment, WLC, attention control, TAU other than standard face-to-face CBT	Computer-assisted, therapist supported vs. self-guided	CBT	Overall: 8 Therapist-supported: 4 Self-guided: 3 Not reported: 1	Overall: 2,807 Therapist-supported:1,243 Self-guided:1,290 Not reported: 274	Overall: g = 0.258 [0.068−0.449] Therapist-supported: g = 0.372 [0.203−0.541] Self-guided: g = 0.038 [−0.083−0.160]	Overall: 85.23 Therapist-guided: 33.38 Self-guided: 35.28	July 2016
Wright et al., 2019	Symptoms of depression	>16	—	WLC, attention control, TAU other than standard face-to-face CBT	Computer-assisted, supported vs. self-guided	CBT	Overall: 40	Overall: 7,198	Overall: g = 0.502 [0.390−0.614] Supported: g = 0.673 [0.546−0.801] Self-guided: g = 0.239 [0.115−0.364]	Overall: 80.23	July 2016
Ye et al., 2014	Anxiety and depression	7−25 years	—	WLC or Face-to Face/Usual care	Online self-help sessions	CBT	7	569	Vs. WLC: SMD = −0.16 [−0.44, 0.12] Vs. F2F:1.32 [0.26, 2.90]	WLC: 53 F2F: 82	January 1990–December 2012

Note. IC = informational control; TAU = treatment-as-usual; WLC = waitlist control; IMI = internet-or-mobile intervention; BAT = behavioral activation therapy; CBT = cognitive behavioral therapy; LRT = life review therapy; DYN = psychodynamic therapy; PST = problem solving therapy; MDD = Major Depressive Disorder; IPDMA = individual participant data meta-analysis; NA = data not available.
[a] Age group, diagnostic criteria.

into a waitlist until pre- and postmeasures were collected). A more recent review by Linardon et al. (2019) found that smartphone-based interventions significantly outperformed control conditions in improving depressive symptoms when active and inactive control conditions were combined (g = .28), yet no significant difference was found when smartphone apps were compared against active control conditions alone. However, both of the aforementioned meta-analyses included studies and interventions not primarily targeting depression (e.g., cognitive training apps, anxiety symptoms, or mental health in general), as well as including samples with and without clinically relevant symptomatology and without relevant cut-off-scores for depressive disorders. As such, the effect of smartphone apps on individuals with elevated levels of depression symptoms remains unclear, as does the effectiveness of smartphone-apps in real-world settings.

Factors Influencing Outcomes of Digital Interventions

As the field has developed over the past decades, an increasing number of studies have examined factors influencing the efficacy of digital interventions. Researchers have identified a broad range of factors moderating outcomes related to (a) participant characteristics, (b) human support, (c) compliance, and (d) study design and quality.

Participant Characteristics

Knowing which participant characteristics determine the outcome of a specific treatment type is crucial if we are to match patients with the right treatments and optimize both efficacy and the efficiency of implementing interventions in the community (Cuijpers et al., 2012; Donker, Batterham, et al., 2013). Although numerous studies have investigated the relationship between individual characteristics such as gender, marital status and education level on intervention outcomes, findings here have been inconsistent and inconclusive (Andersson, 2016; Button et al., 2012; Donker, Batterham, et al., 2013; Spek et al., 2008; Warmerdam et al., 2013). One reason for this may be that RCTs are typically designed to detect overall treatment effects and are underpowered to adequately conduct subgroup and moderator analyses (Brookes et al., 2004). Indeed, meta-analyses using individual participant data (IPD), which provide superior power to detect real differences between subgroups (Cooper & Patall, 2009), have found no effect of gender or education level in moderating the outcomes of digital interventions for depression (Karyotaki et al., 2017; Karyotaki, Ebert, et al., 2018).

Only a few studies have been conducted analyzing the efficacy of digital interventions in specific age groups. In one of the first reviews of Internet- and computer-based cognitive behavioral therapy for anxiety and depression in youth, Ebert et al. (2015) reported significant medium-to-large effect sizes (d = .76) for children, adolescents, and young adults (ages 13–25) when compared with trials with varying control conditions. However, a larger and more recent meta-analysis by Garrido et al. (2019) found only a small effect size for digital interventions compared with inactive control conditions in young people aged 12–25 (d = .33) and no significant difference when interventions were compared with active control conditions. Furthermore, only digital interventions that included regular guidance resulted in moderate effect sizes when compared with inactive control conditions, whereas self-guided interventions were not found to be effective.

Results from studies on digital interventions for the treatment of depression in older adults suggest that digital interventions are effective for this age group. A large RCT of more than 400 participants by Titov and colleagues (2016) that compared a guided versus unguided Internet-based CBT intervention for the treatment of anxiety and depression in older adults (aged 60 years and over) found large reductions in symptoms of depression for participants in both conditions at posttreatment and three-month follow-up. In an IPD meta-analysis of guided Internet-based interventions for depression, Karyotaki, Ebert, et al. (2018) found that effects were greater for older adults compared with younger adults, possibly because of the higher levels of intervention compliance in older adults. Knowing whether digital interventions have comparable outcomes across the life span or whether there is a similar trend toward interventions being more effective in middle- to older-aged population as in psychotherapy (Cuijpers, Karyotaki, et al., 2020) may help inform clinicians about the potential of such treatments for specific age groups. Yet, to our knowledge, no meta-analysis of digital interventions for depression has included studies for all age groups across the life span.

Finally, the question as to whether digital interventions are effective for individuals across all levels of depression severity also has important clinical implications. Several studies have found better outcomes on Internet-based cognitive behavioral therapy (iCBT) for depression for participants with higher baseline severity relative to those with lower baseline symptom scores (Button et al., 2012; Karyotaki et al., 2021; Spek et al., 2008; Warmerdam et al., 2013). An IPD meta-analysis of guided Internet-based interventions for depression by Karyotaki, Ebert, et al. (2018) found that adults with more severe depressive symptoms at baseline were more likely to remit than those with lower depression severity, although the study did not find an association between baseline severity and treatment response. Although most clinical guidelines do not recommend digital interventions as a first-line treatment for individuals with severe depression (NICE, 2017; "Practice Guideline for the Treatment of Patients with Major Depressive Disorder (Revision). American Psychiatric Association.," 2000), further research would benefit from an understanding whether digital interventions are indeed efficacious in the treatment of individuals with high symptom severity.

Human Support

The role of human support or "guidance" is perhaps one of the most widely researched components in digital interventions for depression. Guided interventions refer to interventions that are primarily based on self-help material but accompanied by some form of minimal human guidance delivered via electronic means such as chat or e-mail or via the telephone. Guidance may be related to the therapeutic content itself (e.g., feedback on homework; commonly referred to as 'therapeutic guidance') or focused on fostering compliance (e.g., resolving technical issues related to the intervention or sending reminders to complete intervention modules; commonly referred to as 'technical' or 'motivational guidance'; Ebert et al., 2018).

Several studies have demonstrated that guided interventions lead to greater effect sizes than unguided interventions (Baumeister et al., 2014; Cuijpers, Noma, et al., 2019; Karyotaki et al., 2019, 2021; Königbauer et al., 2017; Wells et al., 2018). In one of the first meta-analyses evaluating the effect of guidance in computer- and

Internet-based interventions for depression, Richards and Richardson (2012) showed a metaregression effect size of $d = .78$ for interventions with therapeutic guidance, compared with $d = .58$ for interventions with technical guidance and $d = .36$ for unguided interventions. In contrast, Baumeister et al. (2014) found no significant differences in effect size when investigating RCTs of Internet-based interventions for depression that directly compared guided versus unguided conditions in the same intervention. Yet, only three studies were included in this subgroup analysis. Baseline depression severity may also moderate the influence of guidance on outcomes. In a large network meta-analysis using individual patient data from 39 studies of iCBT interventions for depression, Karyotaki and colleagues (2021) found that therapeutic guidance was associated with little or no benefit in individuals with mild/subthreshold depression while guided iCBT was associated with superior outcomes in individuals with moderate and severe depression. More recent research has also raised the question as to whether the relative impact of human guidance may be smaller when considering more recently-developed interventions (Shim et al., 2017). Several studies have suggested that "second-generation" self-help interventions that include features specifically designed to improve engagement such as e-mail reminders and responsive design, may produce benefits similar to clinician-guided treatments (Dear et al., 2015, 2016; Fogliati et al., 2016; Titov, Dear, Staples, Terides, et al., 2015). However, there is little evidence from clinical trials comparing technological guidance with human guidance, especially with regards to engagement rates and outcomes in real-word settings.

Another important question relates to the qualification of the person providing the guidance. Prior evidence suggests no difference in outcomes when digital interventions are supported by trained clinicians and when they are supported by nonclinicians in the treatment of individuals with mild-to-moderate symptom severity (Baumeister et al., 2014; Königbauer et al., 2017; Richards & Richardson, 2012; Shim et al., 2017). Such results have significant implications on the public health potential of digital interventions as it may reduce the need for licensed therapists, where availability is already an acute problem in health care. Given the large number of studies that have been published in recent years, we believe there is a timely need for an updated meta-analytic review on guidance that includes the latest studies, together with a thorough exploration of the influence of guidance in different subpopulations (e.g., individuals with higher depression severity), and settings (e.g., clinical vs. community) as well as an analysis of a possible dose-response relationship between guidance and outcomes.

Compliance

One explanation for why guided interventions lead to better therapeutic outcomes than unguided interventions is the higher levels of compliance (often labeled as "adherence" in digital health research) found in the former. Several studies have demonstrated that guided interventions result in higher numbers of completed modules and lower attrition compared with unguided interventions (Baumeister et al., 2014; Donkin et al., 2011; Eysenbach, 2005; Richards & Richardson, 2012). Furthermore, researchers have found a strong dose-response relationship between session completion and effect size in digital interventions, making compliance a critical factor in determining outcomes (Wright et al., 2019). Yet, compliance and engagement with the intervention remains a major challenge in digital interventions (Cuijpers, Noma, et al., 2019; Yardley et al., 2016). One comparison between digital interventions versus face-to-face CBT revealed that the percentage of individuals completing the whole intervention was significantly lower in guided Internet-based CBT compared with face-to-face CBT (65.1% vs. 84.7%). The challenge of intervention compliance may be further exacerbated outside of controlled laboratory settings (Baumel et al., 2019; Graham et al., 2019; Yardley et al., 2016). In one large community-based study of an unguided intervention involving 82,000 users, only 10% of participants completed more than one module (Batterham et al., 2008).

Why some participants comply with the intervention and others do not is unclear. A number of factors have been shown to predict compliance to digital interventions across participant characteristics (including age, gender, lower education level and baseline severity; Christensen et al., 2009; Donkin et al., 2011; Kok et al., 2017) and intervention design (Kelders et al., 2012). Karyotaki et al. (2017) found that compliance was lower in CBT-based interventions compared with interventions based on interpersonal therapy, proposing that CBT without any form of guidance may be relatively demanding. Richards and Richardson (2012) found that computer- and Internet-based interventions with 8 sessions or less led to higher effect sizes than interventions with more than eight sessions. Given that risk of dropout increases significantly beyond a certain number of modules (Eysenbach, 2005), a better understanding of the optimal number and duration of modules across both guided and unguided interventions for maximizing compliance would be of scientific and clinical importance.

Study Design and Quality

As with trials on face-to-face psychotherapy (Cuijpers, 2016a, 2016b; Cuijpers, Berking, et al., 2013), study quality and design have also been shown to significantly influence reported outcomes in trials on digital interventions. A meta-analysis by Andrews et al. (2018) reported a higher mean effect size for studies with low risk of bias than studies where the risk of bias was unclear (.90 vs. .74). In a review of study design and quality in computer- and Internet-based interventions, Arnberg et al. (2014) reported on the lack of proper quality assessment and objective outcome measures, the relatively small sample sizes in most trials, a focus on short-term outcomes, the failure to report on deterioration and adverse events, and the overrepresentation of trials conducted in a limited number of countries threatening generalizability. Given that poor quality trials can lead to a considerable overestimation of effect sizes, a thorough assessment of study design and related risk of bias is critical if we want to avoid drawing false conclusions regarding the efficacy of digital interventions and effect moderating factors.

From Efficacy to Effectiveness: Digital Interventions Beyond the Lab

As the majority of patients with depression are treated in primary care (Bortolotti et al., 2008; Cuijpers, Quero, Dowrick, et al., 2019), a critical question for policymakers and service commissioners is what benefit we can expect to see from digital interventions over and above usual care (Gilbody et al., 2017)? Whereas efficacy trials typically focus on internal validity and pay less attention to the generalizability of the sample population and implementation of the intervention in the real world (Mohr, Weingardt, et al., 2017),

effectiveness trials assess whether findings from efficacy trials can be transferred into routine clinical practice. Here, digital interventions for depression have met with conflicting results.

One of the largest effectiveness studies conducted to-date—the REACCT (Randomised Evaluation of the Effectiveness and Acceptability of Computerised Therapy) trial—found no difference between two well-known Internet-based interventions and general practitioner care as usual, concluding that the benefits of Internet-based interventions may not transfer to clinical settings (Gilbody et al., 2015a). However, the study was met with strong criticism (Gilbody et al., 2015b). In particular, the interventions used in the trial were critiqued for failing to embrace core elements of human-computer-interaction design that may have contributed to the low engagement levels seen in the study (Gilbody et al., 2015b). Furthermore, the amount of guidance provided in the study was extremely low (an average of 6 minutes), which may have also accounted for the fact that only 16–18% of patients completed the entire intervention. Indeed, a follow-up trial, REACCT2 (Gilbody et al., 2017), compared the original intervention arm with another arm that provided regular telephone support (six session between 10 and 20 minutes) and found that the use of the intervention increased by a factor of 1.5-2 and depression scores were significantly lower at follow-up. A more recent study by Richards et al. (2020) demonstrated that an eight-week Internet-based CBT intervention (where those providing guidance were instructed to provide 6 online reviews and spend 15 minutes per participant per review) was significantly more effective than control conditions at posttreatment on both self-report and clinician-rated measures, with statistically significant change also found between posttreatment and 12-month follow-up. However, as the authors of the study pointed out, the use of a waitlist control group may have led to an overestimation of effect sizes compared with care-as-usual, which would have been more reflective of what patients typically experience in the absence of a digital intervention.

These findings raise a number of questions regarding the dissemination of digital interventions beyond highly controlled settings. In particular, whether human guidance is a prerequisite for improved outcomes, what the minimal dose-response relationship may be to establish compliance, how outcomes compare across control conditions, and whether there is a difference in outcomes between different subgroups (e.g., depression severity). To our knowledge, only two meta-analyses have been conducted to-date comparing outcomes between efficacy and effectiveness trials in digital interventions for depression. Andrews et al. (2018) found no significant difference between efficacy and effectiveness trials, concluding that results were congruent with those of efficacy trials. However, the review only included three effectiveness studies targeting depression, several key trials were absent (including the REACCT trial) and the authors only reported on within-group effect size. Wright et al. (2019) compared the outcomes of computer-based CBT for depression in primary care settings versus other settings and found significantly lower effect sizes for the former (g = .22 vs. g = .57). However, the study did not assess whether there were differences in outcomes between control conditions, leaving the central question as to whether digital interventions offer advantages over and above usual care unanswered.

Aims of the Current Systematic Review and Meta-Analysis

The year 2020 marked 30 years since the first article was published on a digital intervention for the treatment of depression (Selmi et al., 1990). It also marked an unparalleled inflection point in the worldwide conversion of mental health services from face-to-face delivery to remote, digital solutions in response to the COVID-19 pandemic. Given the accelerated adoption of digital interventions, it is both timely and important to ask to what extent digital interventions are effective in the treatment of depression, whether they may provide viable alternatives to face-to-face psychotherapy beyond the lab and what are the key factors that moderate outcomes.

The current meta-analysis systematically reviews two decades of research, providing the largest and most comprehensive meta-analysis of digital interventions for the treatment of depression conducted to-date. We aimed to answer the following research questions:

Are Digital Interventions Effective in Reducing Depressive Symptoms?

a. Is there a difference in outcomes between digital interventions and control conditions?

b. Is there a difference in effect size between digital interventions and face-to-face therapy?

c. Does the type of control condition moderate the comparative effect size of digital interventions versus control conditions?

d. Do outcomes differ across delivery methods (smartphone apps versus internet- and computer-based)?

e. Are digital interventions effective in the long-term?

What is the Role of Human Guidance in Influencing Outcomes?

a. Is there a difference in outcomes between unguided interventions and interventions with technical guidance and therapeutic guidance?

b. What is the optimal amount of guidance in improving outcomes?

c. Does the qualification of the individual providing guidance influence outcomes?

Are Digital Interventions Effective 'Beyond the Lab' in Routine Care Settings?

a. Is there a difference in outcomes between efficacy vs effectiveness trial design and, if so,

b. What factors moderate this?

Additionally, we explored what other factors moderate outcomes of digital interventions for depression across patient characteristics (age, gender, somatic comorbidity, and baseline severity levels), intervention components (theoretical orientation, number of sessions), study design and quality (sample size and ROB), and

year of publication (to assess for possible changes in effect size over time).

Method

Search Strategy

We identified studies in a three-step procedure: First, we searched the Cochrane Central Register of Controlled trials (CENTRAL), PsycINFO, EMBASE and MEDLINE for relevant articles. The search was originally conducted on September 13, 2019, and then subsequently on October 13, 2020 during the peer-review process to ensure that the current review included the latest evidence-base. The search string was validated using a sample set of articles from previous meta-analyses (see Appendix A in the online supplemental materials). Second, we checked the reference lists of relevant existing systematic reviews and meta-analyses (Andersson & Cuijpers, 2009; Barak et al., 2008; Baumeister et al., 2014; Carlbring et al., 2018; Cuijpers, Geraedts, et al., 2011; Cuijpers, van Straten, Warmerdam, et al., 2008; Firth, Torous, Nicholas, Carney, Pratap, et al., 2017; Karyotaki et al., 2017; Karyotaki, Ebert, et al., 2018; Königbauer et al., 2017; Linardon et al., 2019; Spek et al., 2007; Weisel et al., 2019). Third and last, we conducted backward searches in all included articles. The full texts of all relevant articles were obtained.

We included studies if (a) they included participants of any age with depressive symptoms, (b) treatment was provided digital via a computer in either an offline or online setting, defined as computerized-, online-, Internet-, web-, or smartphone-based, (c) the study was a randomized controlled trial with an inactive control condition (i.e., waitlist control or no treatment) or active comparison condition (treatment as usual (TAU), attention control, face-to-face psychotherapy), (d) depressive symptomatology was measured by validated self- or clinician-rated depression scales, and (e) elevated depression symptomatology was defined as an inclusion criteria within the study. Inclusion criteria are summarized in Appendix B in the online supplemental materials. The whole selection process was conducted by two independent reviewers (I.M. and P.P., or M.D. and P.P.). The agreement between the reviewers was good in both the title and abstract screening (88.5%, $\kappa = .61$) and full-text assessment (96.5%, $\kappa = .72$). Disagreements were resolved by a discussion among the reviewers. If needed, a third reviewer (L.S.) was consulted.

This systematic review has been registered with the International Prospective Register of Systematic Reviews (PROSPERO CRD42019136554). Further detailed information on the methodology and all procedures for this systematic review and meta-analysis are provided in a study protocol published in advance (Moshe et al., 2020).

Coding Procedures

The data extraction and coding were performed by two independent reviewers (two of I.M., P.P., Y.T., M.D.). All studies were coded for multiple participants, design, intervention, and method features. Any disagreements were solved in discussion. If not indicated otherwise, perfect agreement was reached between the reviewers.

Depression Outcome Measures

In each study all depression outcomes were extracted. This included different outcome measurements (e.g., self-report and clinician ratings) as well as outcomes at different assessment times. The mean and standard deviation for all intervention and control conditions within a study were coded for the calculation of the effect size. For the calculation process see the data analysis section below. Furthermore, the assessment time and instrument were also coded.

Compliance Outcome Measures

In addition to the depression outcomes, compliance was extracted as an outcome. Compliance was extracted for intervention compliance and assessment compliance. The extracted features were the proportion of participants completing assessments, the proportion of participants completing the first intervention module, the average number of intervention modules completed and the proportion of participants completing all modules.

Design and Study Features

We coded the following design and study features: (a) year of publication, (b) type of control group, (c) sample size, (d) region (Asia, Europe, North America, Oceania, multiple, other), and (e) efficacy or effectiveness trial.

Intervention Components

The structure and type of the digital intervention varied across studies. To further describe the interventions used in the study we extracted the (a) type of guidance (unguided, therapeutic guidance [involving therapeutic human support] and technical guidance [which included compliance-focused guidance from a human]), (b) qualification of the guiding personnel ("high," i.e., M.Sc. or Diploma degree in psychology, or professions status as psychotherapist in training, psychotherapist or psychiatrist; "low," i.e., B.Sc., other qualifications or mixed codings), (c) communication mode (synchronous or asynchronous), (d) average guidance time for each participant in minutes, (e) number of intervention modules, and (f) theoretical orientation of the intervention (third-wave, cognitive behavioral therapy, psychodynamic therapy, problem-solving therapy, life-review therapy, other).

Participant Characteristics

We coded (a) age of participants, (b) gender (percentage of females), (c) target population, (d) somatic comorbidities, and (e) baseline severity. Baseline severity was analyzed as a continuous variable to avoid bias resulting from for example, categorization (healthy, mild, severe depression). Of the 17 unique depression scales found in the included studies, the PHQ-9 was the most frequently used scale ($k = 29$, 35%). For all studies reporting baseline severity using PHQ-9, the PHQ-9 was used. One study applied the PHQ-8 and, because of the similarity of both instruments (e.g., $r = .98$ or equivalent clinical cut-offs; Kroenke et al., 2009; Shin et al., 2019), the PHQ-8 score was used for baseline severity in this study. For all other studies, the provided information was recoded to PHQ-9 using two different procedures, depending on the instrument in question. For the Montgomery-Åsberg Depression Rating Scale (MADRS) and Beck Depression Inventory II

(BDI-II) instruments, we used the conversion equations[1] provided by Hawley and colleagues (2013). The applied equations have been shown to have good statistical validity (e.g., Hawley et al., 2013). A total of $k = 21$ (25%) studies were recoded using this procedure. For the ICD-10 Symptom Rating (ISR), Beck Depression Inventory II (BDI-I), Hospital Anxiety and Depression Scale (HADS), Center for Epidemiologic Studies Depression Scale (CES-D), Patient Reported Outcomes Measurement Information System (PROMIS) Depression, Inventory of Depressive Symptomatology (IDS), Quick Inventory of Depressive Symptomatology (QIDS), and Hamilton Depression Rating Scale (HDRS), cross-walk tables were used matching the sum scores of the respective depression instruments to each other based on their underlying latent depression score (theta value based on Item-response theory analysis; Choi et al., 2014; IDS/QIDS, 2021; Wahl et al., 2014). The applied tables have previously been validated and showed strong validity (Choi et al., 2014; Wahl et al., 2014). Recoding using the cross-walk tables was conducted separately by two independent reviewers (YT and PP). For the recoded baseline severity, the agreement between the coders was excellent ICC = .999, 95% CI [.998, 1.000]). The recoded baseline severity ratings of both reviewers were averaged before the analysis to increase objectivity. A total of $k = 30$ (36%) studies were recoded according to this. For two studies using the Edinburgh Postnatal Depression Scale and Mood and Feelings Questionnaire, the above outline procedures were not applicable and the two respective studies were coded as NA. For the extracted data for each study see Appendix C in the online supplemental materials.

Study Quality (Risk of Bias Assessment)

Study quality was assessed by two independent reviewers (two of I.M., P.P., Y.T., M.D.) using the risk of bias tool for randomized trials (RoB; Higgins et al., 2003, 2011). The overall agreement in the RoB between the reviewers was excellent with 85.5% ($\kappa = .73$). Disagreements were resolved by discussion among the reviewers. If needed, a third researcher (L.S.) was consulted to reach consensus. We assessed Risk of Bias for the following domains: (a) "selection bias"; (b) "performance bias"; (c) "detection bias"; (d) "attrition bias"; (e) "reporting bias"; and (f) "other bias." Risk of bias in each domain was judged as "low," "unclear," or "high."

Data Synthesis and Meta-Analysis

Overview of Meta-Analytic Procedures

The present analysis focused on group differences at post between digital interventions and control conditions on symptoms of depression in RCTs. Hedges' g was used as the effect size (ES) to quantify the between-group differences (Hedges, 1981): difference in groups' means were divided by their pooled sample size adjusted standard deviation. Therefore, the means, standard deviations and group sizes were extracted at post for each group. This was also done for baseline to be able to adjust for potential baseline differences. Standard formula for bias correction in small samples ($n < 50$) was applied, if needed (Ellis, 2010; Hedges, 1981). Intention to treat (ITT) data was used in the analysis. As outlined above, studies contained multiple outcomes for depression at multiple assessment time points and partly provided multiple comparators (e.g., different interventions or control types) within the same study. For each of these data points the ES was calculated resulting in dependencies within a study. Hence, we used a three-level metaregression model with random effects to account for the introduced dependencies (Assink & Wibbelink, 2016; Cooper & Hedges, 2009; Pastor & Lazowski, 2018). By assuming a three-level structure we accounted for three different variance components distributed over the three levels in the model. This included sampling variance of the extracted effect sizes at level one; variance between the extracted effect sizes from the same study at level two; and variance between studies at level three (Assink & Wibbelink, 2016). Hence, multiple effect sizes resulting from multiple outcomes, multiple comparison groups or multiple assessments could be included while their dependencies could be accounted for using the three-level structure. This procedure avoids biases caused by the pooling of different effect sizes within a study, where the correlations between outcomes are not reported. For an in-depth overview see Assink and Wibbelink (2016); Cooper and Hedges (2009) and Pastor and Lazowski (2018). In addition, we used cluster-robust standard errors to adjust for potential correlations between effect size estimates (i.e., correlations of level-1 sampling errors; Fernández-Castilla et al., 2021; Pustejovsky, 2021; Pustejovsky & Tipton, 2020).

According to the three-level metaregression model procedure, the average ES of digital interventions was calculated using an intercept-only model. However, to adjust for potential baseline differences (e.g., introduced by postrandomization attrition) we included baseline differences as a covariate throughout the analyses. Afterward, different subsets and metaregression was used to quantify the influence predictors, controlled for baseline differences, if not otherwise indicated. Profile likelihood plots were used to check for overparameterization and identifiability. A subset was defined to investigate the average ES in each control type. In addition, we used metaregression to assess the ES of digital interventions in active and inactive control conditions. Similarly, we estimated the ES for each delivery modality and tested for significant differences. In addition, the three-level structure allows for the inclusion of multiple assessment points (e.g., post, six months, and 12 months follow-up assessment) from the same study. To answer the question of long-term efficacy and effectiveness of digital interventions, metaregression with assessment time as predictor was conducted. We tested for a linear, quadratic, and cubic change in ES over assessment time.

A second major focus of the present study was to investigate the role of guidance on the ES of digital interventions. We used the following operational definitions of guided and unguided interventions: In unguided interventions no human support was involved and thus interventions can be considered as fully self-guided interventions. In guided interventions with technical and compliance-facilitating support, the main goal of support was to solve technical problems and facilitate the motivation and compliance of patients to the intervention; essentially, the technologically delivered human support offered was not intended to be therapeutic itself and did not deal with therapeutic process-related aspects. In contrast, in interventions with therapeutic guidance, the main focus of technology-mediated human support was dedicated to

[1] PHQ = 3.126 + .523 × MADRS; PHQ = −12.07 + .489 × SRS; PHQ = 2.308 + .422 × BDI (Hawley et al., 2013).

content and processes related to the treatment and was of a genuine therapeutic nature. To distinguish between the different types of guidance provided, we also extracted the professions and qualification of the persons implementing the guidance—as well as information on supervision, the amount of guidance and communication mode—to reflect the plethora of approaches used to deliver guidance in digital interventions for depression globally and to enable more fine-grained analyses related to the role of guidance. Importantly, to categorize the type of guidance, we focused exclusively on the a priori operationalizations of guidance as stated in the publications of primary studies rather than the actual uptake and usage of guidance by patients. The average ES for each type of guidance was explored. Moreover, we tested for significant differences in outcomes between interventions with technical guidance compared with unguided interventions and interventions with therapeutic guidance compared with unguided interventions using metaregression. In the latter subset of unguided and therapeutic guided digital interventions, we tested also for an interaction of the guidance effect with (a) qualification of guiding personnel and (b) guidance time. The third research question within this study was whether digital interventions are effective in routine care (i.e., effectiveness) settings. To answer this question and provide a comparison of ES between efficacy and effectiveness settings, we separately calculated the average ES in efficacy and effectiveness studies and tested for differences using the metaregression approach.

Additionally, we used metaregression to assess the following moderators:(a) pretreatment depression severity,(b) somatic comorbidities, (c) gender, (d) age, (e) therapeutic approach, (f) number of modules, (g) study quality (item-wise RoB), and (h) year of publication.

Last, we explored intervention compliance using a three-level random effects metaregression model. Intervention compliance was defined in two ways: (a) as the percentage of participants that completed all modules (= completer rate) and (b) the average percentage of modules completed by a participant (= module completion rate). A subset for each of these definitions was used. Only studies reporting information on intervention compliance were included, respectively. As in the models for effect size, the influence of moderators was explored with metaregression. We also explored the influence of compliance on ES in the two subsets.

All analyses were conducted using R (R Development Core Team, 2016). The *metafor* package was the primary analysis package (Pastor & Lazowski, 2018; Viechtbauer, 2010).

Study Heterogeneity and Variance Components

Heterogeneity was calculated using the I^2 statistic (Borenstein et al., 2017). Profile likelihood confidence intervals were also calculated (Borenstein et al., 2017; Jackson et al., 2014). A value of 0% indicates no heterogeneity and higher values indicate higher heterogeneity. A heterogeneity of 25% is defined as the threshold for low, 50% for moderate and 75% for high heterogeneity (Ioannidis et al., 2007). We expected high heterogeneity based on the findings of previous meta-analyses and the extended time frame in the present study. In addition, we reported the variance components for level 2 (σ^2_{within}) and level 3 ($\sigma^2_{between}$) to quantify the between- and within-study heterogeneity (Borenstein et al., 2017; Konstantopoulos, 2011).

Small Study Effects and Publication Bias

To detect small study effects or potential publication bias we used the following methods: First, we used a funnel plot visualizing the ES against the precision (standard error [*SE*]). Asymmetry would indicate an influence of precision on the ES and potential bias. Second, the potential influence of precision was tested using the Egger's test adapted to the three level structure of the present meta-analysis (Egger et al., 1997; Fernández-Castilla et al., 2021). However, instead of the standard error, we used the weight as a predictor in the metaregression model, because using *SE* tends to overreject due to artifactual correlations with ES (Pustejovsky & Rodgers, 2019). Third, we used significance funnel plot visualizing the extent to which ES in nonaffirmative studies' (nonsignificant ES or ES favoring control) are systematically smaller than the entire set of ES estimates (Mathur & VanderWeele, 2020). The ES based on nonaffirmative studies provided an approximation for the ES in case of maximal publication bias. In addition, we calculated publication bias-corrected ES under robust random-effects specifications according to procedures outlined in Mathur and VanderWeele (2020) for varying degrees of publication bias (η = 1 to 50, where η indicates the increased likelihood for affirmative findings to be published).

Results

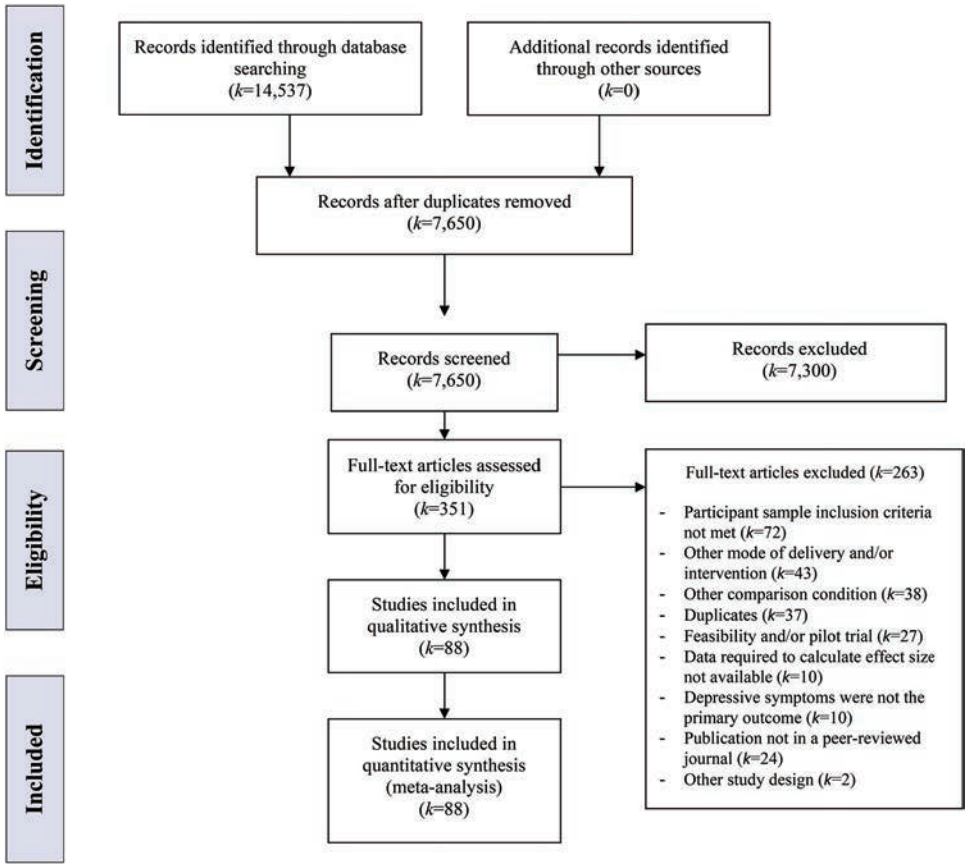
Study Characteristics

Our search yielded 14,513 articles (CENTRAL = 3,711; Embase = 4,333; Medline = 3,764; PsycINFO = 2,705). After the removal of duplicates, we assessed a total of 7,651 studies by title and abstract, of which 351 were considered potentially relevant. After full-text assessment, 88 published article covering 83 unique studies met the inclusion criteria and were included (see Figure 1). The first study in the field of digital interventions was published in 1990 (Selmi et al., 1990). Interestingly, we found no other study published in the first decade. However, the field has grown rapidly since 2000: Ten studies were published during the second decade (2000–2009) and in the last decade, 72 studies were published (2010–2020). See Table 2 for selected characteristics of the included studies.

Overall N = 15,530 individuals participated in the included studies. Most of the studies focused on adult populations (k = 79, 95%). The mean age across all studies was M = 41.33 (SD = 9.68). Women were represented more frequently in the included RCTs (M = 69.5%, SD = 15.3%). Moreover, the included studies mainly focused on individuals with mild to moderate depression symptom severity (recoded PHQ-9: M = 12.91, SD = 2.95). Studies were predominantly conducted in western cultures: Europe (k = 51, 61%), North America (k = 15, 18%). and Australia and New Zealand (k = 13, 16%). Only three of the included studies were conducted in Asia (4%) and one study in South America (1%). We found no studies conducted in Africa.

Cognitive behavioral therapy served most often as the theoretical orientation in digital interventions (k = 67, 74.4%), followed by third-wave (k = 9, 10.0%), problem-solving therapy (k = 7, 7.8%), psychodynamic therapy (k = 1, 1.1%), life review therapy (k = 1, 1.1%), and other (k = 5, 5.6%; e.g., combined approaches). Most digital interventions were accompanied by some form of guidance (k = 72, 80.0%; therapeutic guidance: k = 47, 52.2;

Figure 1
Flow of Study Reports Into the Research Synthesis



Note. See the online article for the color version of this figure.

technical guidance: k = 25, 27.8%), whereas k = 18 interventions were unguided (20.0%). The average number of modules was M = 7.4 (SD = 2.1). For a summary of the study characteristics see Table 3.

Study Quality (Risk of Bias Assessment)

The risk of bias assessment identified "sequence generation" (low: k = 75, 90.4%; unclear: k = 5, 6.0%; high: k = 3, 3.6%) and "other biases" (low: k = 78, 94.0%; unclear: k = 2, 2.4%; high: k = 3, 3.6%) as the least sources of risk of bias. "Allocation concealment" was also low in the majority of studies (k = 61, 73.5%; unclear: k = 19, 22.9%; high: k = 3, 3.6%). Risk of bias due to "selective outcome reporting" was rated low in 59 studies (71.1%) and unclear in 24 (28.9%). Regarding "incomplete data handling," 55 studies (66.2%) were rated as low, 3 (3.6%) as unclear, and 25 (30.1%) as high. Risk of bias from "blinding of participants" was rated high for most studies (low: k = 0, 0%; unclear: k = 16, 19.27%; high: k = 67, 80.72%) as was the risk of bias for "blinding of outcome assessors" (low: k = 7, 7.23%, unclear: k = 17, 20.48%; high: k = 60, 72.3%). In psychotherapy research the complete masking of participants (and personnel providing therapeutic support) is generally not feasible (Munder & Barth, 2018) and self-report ratings might therefore be prone to bias; thus, we rated self-reports with a high risk of bias on the "blinding of outcome assessors" domain in most instances. However, it may be conceivable that in pure self-help interventions (without any guidance) participants might be unaware of the intervention condition they receive, especially when there are two active comparison conditions. Finally, RoB item-wise comparison between low-risk studies against high-risk studies showed no differences in the ES (all $p > .05$). A summary of the risk of bias across all studies appears in Figure 2.

Are Digital Interventions Effective in Reducing Depressive Symptoms?

The k = 83 included studies provided a total of 121 comparisons between digital interventions and any control group at posttreatment. The average effect size of digital interventions compared with any control group adjusted for baseline differences was g = .52,95% CI [.43, .60], $p < .001$; forest plot presented in Appendix D in the online supplemental materials). Heterogeneity was high: I^2 = 84, 95% CI [57, 100]; $\sigma^2_{within} \leq .001$, 95% CI [.00, .006], $\sigma^2_{between}$ = .126, 95% CI [.086, .189]. See Table 4 for details on effect sizes of interventions when compared with different control conditions.

The majority of included studies used cut-off-based inclusion criteria (k = 51, 61.4%). Only k = 32 (38.55%) studies required a clinical diagnosis of any depressive disorder and, of these, k = 22 (26.5%)

Table 2
Selected Characteristics of Studies of Digital Interventions for Depression

Study	*N*	*M* Age (*SD*)	Control	Outcome measure	Delivery method	Guidance type	Hedge's *g*	Intervention completion rate (%)	% Completors	Country
Andersson et al. (2005)	117	36.35 (10.71)	WLC	BDI	Internet	GS	0.97	74.0	65.0	SE
Andersson et al. (2013)	69	42.3 (13.5)	gF2F	MADRS-S	Internet	GS	0.39	96.9	87.9	SE
Baumeister et al. (2021)	209	49.9 (9.36)	TAU	HRSD-17	Internet	GS	0.25	—	55.0	DE
Beevers et al. (2017)	376	31.91 (11.2)	WLC	QIDS-SR	Internet	TG	0.82	—	—	US
Beiwinkel et al. (2017)	180	47.74 (10.92)	ATT	PHQ-9	Internet	GS	0.39	—	—	DE
Berger et al. (2011)	51	38.91 (14.16)	WLC	BDI-II	Internet	GS	1.14	85.2	56.0	Multiple
Berger et al. (2011)	51	39.11 (13.71)	WLC	BDI-II	Internet	UG	0.66	68.0	36.0	Multiple
Birney et al. (2016)	300	—	ATT	PHQ-9	Smartphone	TG	0.14	—	—	US
Boele et al. (2018)	89	44.99 (11.99)	WLC	CES-D	Internet	GS	0.63	—	—	NL
Boeschoten et al. (2017)	171	48.9 (10.5)	WLC	BDI-II	Internet	GS	0.08	—	50.6	NL
Buntrock et al. (2015)	406	45.04 (11.89)	ATT	CES-D	Internet	GS	0.66	82.2	68.3	DE
Carlbring et al. (2013)	80	44.4 (13.5)	WLC	MADRS-S	Internet	GS	0.64	72.9	27.5	SE
Choi et al. (2012)	55	39 (11.7)	WLC	CBDI	Internet	GS	0.91	69.5	68.0	ANZ
Christensen et al. (2004)	360	36.07 (9.4)	ATT	CES-D	Internet	TG	0.33	51.0	—	ANZ
Clarke et al. (2002)	299	44.35 (12.2)	TAU	CES-D	Internet	UG	0.25	37.1	—	US
Clarke et al. (2005)	175	47.27 (10.8)	TAU	CES-D	Internet	TG	0.06	84.3	—	US
Clarke et al. (2005)	180	44.73 (10.5)	TAU	CES-D	Internet	TG	−0.20	84.3	—	US
Clarke et al. (2009)	160	22.65 (2.3)	TAU	PHQ-8	Internet	UG	0.16	—	—	US
De Graaf et al (2009, 2011)	203	44.71 (12)	TAU	BDI-II	Internet	UG	0.15	42.5	14.0	NL
Deady et al. (2016)	104	21.74 (2.22)	ATT	PHQ-9	Internet	UG	0.46	37.5	—	ANZ
Ebert et al. (2014)	150	47.1 (8.2)	WLC	CES-D	Internet	GS	0.69	—	60.0	DE
Ebert et al. (2017)	256	50.8 (11.8)	ATT	CES-D	Internet	GS	0.89	—	61.5	DE
Ebert et al. (2018)	204	44.2 (11.73)	WLC	QIDS-C	Internet	GS	0.40	83.3	61.8	DE
Farrer et al. (2011)	73	40.47 (12.13)	TAU	CES-D	Internet	UG	0.78	30.0	15.8	ANZ
Farrer et al. (2011)	80	42.58 (12.2)	TAU	CES-D	Internet	TG	1.08	40.0	17.8	ANZ
Fischer et al. (2015)	90	45.28 (11.99)	WLC	BDI	Internet	UG	0.33	—	—	DE
Flygare et al. (2020)	95	45.3 (12.2)	ATT	MADRS-S	Internet	GS	0.23	73.8	—	SE
Forand et al. (2018)	89	—	WLC	PHQ-9	Internet	GS	1.61	77.8	55.9	US
Forsell et al. (2017)	42	31.01 (4.57)	TAU	MADRS-S	Internet	GS	1.18	53.0	—	SE
Geraedts, Kleiboer, Twisk, et al. (2014), Geraedts, Kleiboer, Wiezer, et al. (2014)	231	43.4 (9.2)	TAU	CES-D	Internet	GS	0.25	—	27.6	NL

(*table continues*)

Table 2 (*continued*)

Study	*N*	*M* Age (*SD*)	Control	Outcome measure	Delivery method	Guidance type	Hedge's *g*	Intervention completion rate (%)	% Completors	Country
Gilbody et al. (2015a)	481	39.97 (12.81)	TAU	PHQ-9	Internet	TG	−0.01	—	12.0	UK
Gilbody et al. (2015a)	449	—	TAU	PHQ-9	Internet	TG	−0.05	—	14.8	UK
Gladstone et al. (2018)	369	15.4 (1.5)	ATT	CES-D	Internet	TG	−0.28	22.7	—	US
Gladstone et al. (2018)	369	15.4 (1.5)	ATT	CES-D	Internet	TG	−0.06	22.7	—	US
Glozier et al. (2013)	562	57.95 (6.6)	ATT	PHQ-9	Internet	TG	0.16	—	—	ANZ
Guo et al. (2020)	300	28.3 (5.8)	WLC	CES-D	Smartphone	TG	0.63	55.0	—	CN
Hallgren et al. (2015)	629	43 (12)	TAU	MADRS-S	Internet	GS	0.33	60.0	—	SE
Ip et al. (2016)	257	14.63 (0.81)	ATT	CES-D-R	Internet	TG	−0.01	30.0	10.1	CN
Johansson, Ekbladh, et al. (2012)	92	45.6 (14)	other	BDI-II	Internet	GS	1.12	—	78.3	SE
Johansson, Sjöberg, et al. (2012)	79	44.28 (12.72)	ATT	BDI-II	Internet	GS	0.56	80.7	—	SE
Johansson, Sjöberg, et al. (2012)	78	45.22 (11.39)	ATT	BDI-II	Internet	GS	0.83	77.2	—	SE
Johansson, Bjärehed, et al. (2019)	54	—	WLC	MADRS-S	Internet	GS	1.27	78.8	54.0	SE
Johansson, Westas, et al. (2019)	144	63 (12)	ATT	PHQ-9	Internet	TG	0.44	—	59.7	SE
Kenter et al. (2016)	269	38 (11.4)	ATT	CES-D	Internet	GS	−0.07	—	12.5	NL
Kivi et al. (2014)	79	36.6 (11.3)	TAU	BDI-II	Internet	GS	0.12	72.9	55.6	SE
Lamers et al. (2015)	116	57.09 (9.16)	WLC	CES-D	Internet	GS	0.35	—	—	NL
Lappalainen et al. (2014)	38	44.61 (14.28)	F2F	BDI-II	Internet	GS	−0.15	—	—	FI
Lappalainen et al. (2015)	39	51.9 (12.88)	WLC	BDI-II	Internet	GS	0.61	97.4	94.7	FI
Levin et al. (2011)	191	43.52 (12.93)	TAU	CES-D	Computer	TG	0.44	—	—	US
Löbner et al. (2018)	647	43.89 (13.29)	TAU	PHQ-9	Internet	UG	0.00	—	9.1	DE
Lokman et al. (2017)	329	43.25 (12.94)	WLC	IDS-SR	Internet	UG	0.42	—	—	NL
Meyer et al. (2015)	163	42 (11.39)	TAU	PHQ-9	Internet	UG	0.57	—	—	DE
Meyer et al. (2019)	200	40.3 (13.12)	WLC	PHQ-9	Internet	UG	0.54	—	—	DE
Milgrom et al. (2016)	43	31.6 (4.44)	TAU	BDI-II	Internet	GS	0.81	—	85.7	ANZ
Mira et al. (2017)	80	35.91 (9.94)	WLC	BDI-II	Internet	UG	0.50	73.0	77.8	ES
Mira et al. (2017)	88	35.77 (9.78)	WLC	BDI-II	Internet	TG	0.35	73.0	77.8	ES
Montero-Marin et al. (2016)	198	43.11 (9.49)	TAU	BDI-II	Internet	GS	0.08	—	—	ES
Montero-Marin et al. (2016)	200	42.81 (10.84)	TAU	BDI-II	Internet	UG	0.12	—	—	ES
Moritz et al. (2012)	210	38.57 (13.75)	WLC	BDI	Internet	UG	0.43	63.2	—	DE
Newby et al. (2017)	90	46.7 (12.6)	WLC	PHQ-9	Internet	GS	0.79	—	65.9	ANZ
Nobis et al. (2015)	256	51 (12)	ATT	CES-D	Internet	GS	0.89	—	62.0	DE
Noguchi et al. (2017)	651	43.85 (11.3)	WLC	CES-D	Internet	UG	−0.02	—	—	JP

(*table continues*)

Table 2 (*continued*)

Study	*N*	*M* Age (*SD*)	Control	Outcome measure	Delivery method	Guidance type	Hedge's *g*	Intervention completion rate (%)	% Completors	Country
Nygren et al. (2019)	50	33.86 (8.12)	WLC	BDI-II	Internet	GS	1.23	62.9	36.0	SE
Oehler et al. (2020)	347	—	ATT	IDS-SR	Internet	TG	0.23	91.7	—	DE
O'moore et al. (2018)	69	61.9 (6.92)	TAU	PHQ-9	Internet	TG	1.02	—	84.1	ANZ
Perini et al. (2009)	45	49.29 (12.06)	WLC	PHQ-9	Internet	GS	0.83	—	74.1	ANZ
Pfeiffer et al. (2020)	330	51.6 (14.9)	TAU	QIDS-SR	Internet	GS	0.14	47.5	—	US
Pots et al. (2016)	169	46.9 (11.77)	WLC	CES-D	Internet	GS	0.56	—	73.0	NL
Pugh et al. (2016)	50	—	WLC	EPDS	Internet	GS	1.04	84.6	60.0	CA
Reins et al. (2019)	131	41.6 (10.8)	ATT	HRSD-24	Internet	GS	0.32	—	75.4	DE
Richards et al. (2015)	188	39.86 (10.92)	WLC	BDI-II	Internet	GS	0.65	—	36.0	UK
Roepke et al. (2015)	186	—	WLC	CES-D	Smartphone + Internet	UG	0.31	—	—	US
Rosso et al. (2017)	77	28.99 (7.21)	ATT	HRSD-17	Internet	TG	0.79	—	91.9	US
Ruwaard et al. (2009)	54	42 (9.51)	WLC	BDI-IA	Internet	GS	0.84	—	—	NL
Salamanca-Sanabria et al. (2020)	214	22.15 (4.7)	WLC	PHQ-9	Internet	TG	0.88	—	9.3	CO
Sander et al. (2020)	295	52.8 (7.7)	TAU	PHQ-9	Internet	GS	0.42	67.5	0.5	DE
Schure et al. (2019)	343	42.9 (13.3)	WLC	PHQ-9	Smartphone + Internet	TG	0.50	28.1	—	US
Segal et al. (2020)	460	48.3 (14.9)	TAU	PHQ-9	Internet	TG	0.55	60.0	27.4	CA
Selmi et al. (1990)	24	29.9 (4.41)	WLC	BDI	Computer	TG	1.00	100.0	100.0	US
Selmi et al. (1990)	24	—	F2F	BDI	Computer	TG	0.18	100.0	100.0	US
Selmi et al. (1990)	24	29.9 (4.4)	WLC	BDI	Computer	TG	1.67	100.0	100.0	US
Smith et al. (2015)	112	—	WLC	MFQ-C	Computer	UG	0.82	—	85.5	UK
Smith et al. (2017)	113	39.94 (12.96)	WLC	PHQ-9	Internet	TG	0.87	—	59.3	ANZ
Spek et al. (2007)	202	55 (4.95)	WLC	BDI-II	Internet	UG	0.27	78.1	48.3	NL
Spek et al. (2007)	201	55 (4.95)	gF2F	BDI-II	Internet	UG	−0.06	78.1	48.3	NL
Titov et al. (2010)	86	42.79 (12.91)	WLC	PHQ-9	Internet	GS	1.27	—	69.6	ANZ
Titov et al. (2010)	81	44.99 (12.92)	WLC	PHQ-9	Internet	TG	1.27	—	80.5	ANZ
Titov et al. (2015)	52	—	WLC	PHQ-9	Internet	GS	2.29	—	70.0	ANZ
Ünlü Ince et al. (2013)	96	35.2 (9.3)	WLC	CES-D	Internet	GS	1.51	—	20.4	NL
van Luenen et al. (2018)	188	46.3 (10.63)	ATT	PHQ-9	Internet	TG	0.61	—	—	NL
Vernmark et al. (2010)	58	34.95 (11.86)	WLC	BDI	Internet	GS	0.57	85.7	58.6	SE
Wagner et al. (2014)	62	—	F2F	BDI-II	Internet	GS	−0.01	—	78.1	CH
Warmerdam et al. (2008)	175	—	WLC	CES-D	Internet	GS	0.47	—	37.5	NL
Warmerdam et al. (2008)	175	—	WLC	CES-D	Internet	GS	0.26	—	38.6	NL
Williams et al. (2013)	63	44.76 (12.05)	WLC	BDI-II	Internet	GS	0.97	—	54.3	ANZ
Wright et al. (2017)	91	15.35 (1.3)	ATT	BDI	Computer	TG	0.00	—	62.2	UK

Note. WLC = Waiting list control; gF2F = group Face-to-Face; TAU = Treatment as usual; ATT = attention; GS = guided service; TG = technical guidance; UG = unguided.

Table 3
Descriptive Summary of the Characteristics of the Studies Included in the Meta-Analysis (k = 83)

Name	Total
Number of studies	83
Participant characteristics	
Age *M* (*SD*)	41.3 (9.7)
Females	69.5%
Target populations	
Children and adolescents	5 (6%)
Adults	76 (91.6%)
Older adults (>50 years)	2 (2.4%)
Baseline severity (PHQ-9)	12.9 (2.9)
Comorbid diseases	15 (18.1%)
Intervention characteristics	
Guidance	
Therapeutic	47 (52.2%)
Technical	25 (27.8%)
Unguided	18 (20.0%)
Number of modules	7.3 (2.2)
Theoretical orientation	
Third-wave	9 (10.0%)
CBT	67 (74.4%)
LRT	1 (1.1%)
DYN	1 (1.1%)
PST	7 (7.8%)
Other	5 (5.6%)
Study design	
Passive control	
Wait-list control	43 (46.7%)
Active control conditions	
Treatment as usual	24 (26.1%)
Attention control	19 (20.7%)
Face-to-face	3 (3.2%)
Group face-to-face	2 (2.2%)
Other[a]	1 (1.1%)
Setting	
Efficacy	62 (74.7%)
Effectiveness	21 (25.3%)
Sample size	
Total *N*	15,530
M (*SD*)	173.4 (148.0)
Location	
Europe	51 (61%)
Australia & New Zealand	13 (16%)
North America	15 (18%)
Asia	3 (4%)
Africa	0 (0%)
South America	1 (1%)

Note. CBT = cognitive behavioral therapy; LRT = life review therapy; DYN = psychodynamic therapy; PST = problem solving therapy.
[a] Psychoeducation with weekly guidance (Johansson, Ekbladh, et al., 2012).

included only patients with Major Depressive Disorder. In the subset of any depressive disorder the ES was $g = .52$, 95% CI [.37, .66], $p < .001$; $I^2 = 79$, 95% CI [44, 100]; $\sigma^2_{within} \leq .001$, 95% CI [.00, .012], $\sigma^2_{between} = .130$, 95% CI [.072, .245], whereas in the subset of MDD patients the ES was $g = .59$, 95% CI [.40, .78], $p < .001$; $I^2 = 79$, 95% CI [40, 100]; $\sigma^2_{within} \leq .001$, 95% CI [.00, .022], $\sigma^2_{between} = .155$, 95% CI [.078, .331]. Hence, digital interventions were shown to be effective both in for participants with elevated depressive symptoms and in participants with a formal diagnosis of depression.

Is There a Difference in Effect Size Between Digital Interventions and Face-to-Face Therapy?

Only three comparisons from three studies were available comparing digital interventions and individual face-to-face therapy, all of which involved interventions with human guidance. The comparison adjusted for baseline differences indicated there was a nonsignificant difference to face-to-face therapy of $g = -.01$, 95% CI [−2.73, 2.72], $p = .982$; $I^2 < .001$, 95% CI [.00, 100]; $\sigma^2_{within} =$ fixed, $\sigma^2_{between} < .001$, 95% CI [.000, 9.195]. For group face-to-face therapy we identified only two studies, which provided a total of three data points at post. Again, based on this limited evidence, there was no significant difference (unadjusted for baseline difference, owing to convergence; $g = .17$, 95% CI [−2.91, 3.26], $p = .609$); $I^2 = 69$, 95% CI [.00, 100]; $\sigma^2_{within} \leq .001$, 95% CI [.000, .976], $\sigma^2_{between} = .093$, 95% CI [.000, > 10.000].

Does the Type of Control Condition Moderate the Comparative Effect Size of Digital Interventions Versus Control Condition?

The type of control condition varied across the included studies and included passive (= WLC) and active (e.g., attention) control conditions. Overall, the number of between-group comparisons between the intervention group and passive control conditions (WLC: $n = 57$, 47.1%) and active control conditions (total: $n = 64$, 52.9%; TAU: $n = 26$; attention control: $n = 29$; individual F2F: $n = 3$; group F2F: $n = 3$; other: $n = 3$) were almost equal. Using meta-regression to assess whether the type of control condition moderated reported outcomes, we identified that the control type (active vs. passive) significantly influenced ES, explaining 22.4% of the variance between studies. Studies with passive control conditions showed a significant higher between-group ES than studies with active control conditions ($\beta = .35$, 95% CI [.21, .49], $p < .001$). For the subset of WLC comparisons, the between-group ES was medium-to-large with a pooled ES of $g = .70$. 95% CI [.58, .83], $p < .001$; $I^2 = 79$, 95% CI [43, 100]; $\sigma^2_{within} < .001$, 95% CI [.000, .014], $\sigma^2_{between} = .118$, 95% CI [.065, .219]. Digital interventions also outperformed active control conditions, $g = .35$, 95% CI [.26, .45], $p < .001$; $I^2 = 80$, 95% CI [54, 100]; $\sigma^2_{within} < .001$, 95% CI [.000, .005], $\sigma^2_{between} = .098$, 95% CI [.066, .149]. However, the effect was small-to-medium. Further sensitivity analyses were conducted to provide an average ES for each active control type. When compared with attention control conditions, the average ES for digital interventions was $g = .36$, 95% CI [.19, .54], $p < .001$; $I^2 = 84$, 95% CI [41, 100]; $\sigma^2_{within} < .001$, 95% CI [.000, .023], $\sigma^2_{between} = .104$, 95% CI [.051, .236] and in treatment as usual control conditions the average effect was $g = .31$, 95% CI [.21, .41], $p < .001$; $I^2 = 60$, 95% CI [0, 100]; $\sigma^2_{within} < .001$, 95% CI [.000, .027], $\sigma^2_{between} = .026$, 95% CI [.000, .098]. The forest plots for the ES of digital interventions compared with all control types are presented in Appendices E–H in the online supplemental materials.

Do Outcomes Differ Across Delivery Methods?

Most included studies used the Internet for the delivery of the intervention ($k = 75$, 90.36%). Only four studies (4.82%) reported on the ES of computer-based interventions, two on smartphone-

Figure 2
Summary of Risk of Bias

Note. See the online article for the color version of this figure.

based apps and Internet combined interventions (2.41%), and two on interventions using smartphone-based apps exclusively (2.41%). When comparing to all control conditions, the average ES in Internet-based intervention was $g = .53$, 95% CI [.43, .62], $p < .001$; $I^2 = 85$, 95% CI [57, 100]; $\sigma^2_{within} < .001$, 95% CI [.000, .000], $\sigma^2_{between} = .138$, 95% CI [.092, .210], computer-based ES was $g = .45$, 95% CI [−.42, 1.31], $p = .151$; $I^2 = 62$, 95% CI [0, 100]; $\sigma^2_{within} = .108$, 95% CI [.000, 1.548], $\sigma^2_{between} < .000$, 95% CI [.000, 1.95], and smartphone-based interventions (combining smartphone exclusive and enhanced interventions) showed a superiority of $g = .39$, 95% CI [−.27, 1.06], $p = .122$; $I^2 = 80$, 95% CI [2, 100]; σ^2_{within} fixed to zero, $\sigma^2_{between} = .054$, 95% CI [.002, 1.181]. Although the point estimates indicated that computer-based and smartphone-based interventions may be inferior to

Table 4
Effects of Psychotherapies Across Different Types of Control Conditions: Hedges' g

Control type	*g*	95% CI	*p* value	I^2	σ^2_{within}	$\sigma^2_{between}$
All control conditions	0.52	[0.43, 0.60]	<.001	84 (57 to 100)	<0.001 (0.000 to 0.006)	0.126 (0.086 to 0.189)
Passive control conditions						
WLC	0.70	[0.58, 0.83]	<.001	79 (43 to 100)	<0.001 (0.000 to 0.014)	0.118 (0.065 to 0.219)
Active control conditions						
TAU	0.31	[0.21, 0.41]	<.001	60 (0 to 100)	<0.001 (0.000 to 0.037)	0.026 (0.000 to 0.098)
Attention	0.36	[0.19, 0.54]	<.001	84 (41 to 100)	<0.001 (0.000 to 0.023)	0.104 (0.051 to 0.236)
Face-to-face	−0.01	[−2.73, 2.72]	.982	<.001 (0.00 to 100)	0 (fixed)[a]	<0.001 (0.000 to 9.195

Note. Hedges *g* according to the random-effects model. WLC = waitlist control; TAU = treatment-as-usual.
[a] Only one effect size per study, hence within-study variance was fixed to zero.

Internet-based interventions, metaregression did not show any significant differences ($p > .05$). However, only one trial (Guo et al., 2020) indicated the efficacy of a stand-alone smartphone app intervention on the reduction of depressive symptoms. Notably, none of the computer-based or smartphone-based interventions involved therapeutic guidance.

Are Digital Interventions Effective in the Long Term?

The three-level metaregression enables the estimation of continuous predictors. Since the included studies provided a broad range of assessment times, we evaluated whether the assessment time influenced the effect size of digital interventions compared with control conditions. However, 95% of all comparisons did not extend further than a one-year follow-up. Hence, we included only data points up to one-year. We did not identify a significant decrease in ES within a one-year period (linear, quadratic, and cubic effects: $p > .05$).

What Is the Role of Human Guidance on Influencing Outcomes?

We calculated the average ES separately for the three types of guidance distinguished in the present study: unguided, technical guidance, and human therapeutic guidance. In the subset of unguided interventions, the average effect of digital interventions compared with all control conditions and adjusted for baseline differences was $g = .34$, 95% CI [.24, .45], $p < .001$; $I^2 = 58$, 95% CI [0, 100]; $\sigma^2_{within} < .001$, 95% CI [.000, .052], $\sigma^2_{between} = .025$, 95% CI [.000, .078]. For interventions with technical guidance, we found an average effect of $g = .46$, 95% CI [.29, .62], $p < .001$; $I^2 = 88$, 95% CI [46, 100]; $\sigma^2_{within} < .001$, 95% CI [.000, .024], $\sigma^2_{between} = .134$, 95% CI [.070, .277] compared with all control conditions. Using metaregression to compare therapeutic guidance (TG) and unguided (UG) interventions yielded a nonsignificant difference, $\beta = .11$, 95% CI [−.07, .28], $p = .225$. The effect of guided interventions with human therapeutic guidance was $g = .63$, 95% CI [.50, .76], $p < .001$; $I^2 = 82$, 95% CI [48, 100]; $\sigma^2_{within} < .001$, 95% CI [.000, .013], $\sigma^2_{between} = .155$, 95% CI [.090, .272]. Compared with unguided interventions, the incremental effect gained by human therapeutic guidance was $\beta = .22$, 95% CI [.03, .41], $p = .024$. For the corresponding forest plots see Appendices I–K in the online supplemental materials.

We investigated the communication mode, qualification and duration of guidance as moderators of the influence of therapeutic guidance on outcomes. In the guided interventions therapeutic support was delivered synchronously in 10 instances and asynchronously in 37 instances (and 20 mixed). Comparing studies with synchronous versus asynchronous guidance, we did not find differences in ES between the two modes ($\beta = .20$, 95% CI [−3.66, 3.26], $p = 659$). A total of 65 comparisons at postassessment included a human guided intervention. In 21 (32.3%) of these, guidance was provided by highly qualified clinicians with either a Masters-level degree in psychology, diploma in psychology, psychotherapist (in training included) or psychiatrist qualification. High qualification level compared with low did not impact the effect of guidance on ES ($\beta = .17$, 95% CI [−12, .46], $p = 254$). The average minutes of guidance in the human guided interventions were $M = 80.93$ with a large standard deviation of $SD = 38.44$. Metaregression showed no time and guidance interaction ($\beta = -.00$, 95% CI [−.01, .01], $p = .316$).

Lastly, we investigated whether guidance impacted the long-term ES of digital interventions across all control conditions in a one-year period. Although the ES for guided interventions was significantly higher compared with unguided ($\beta = .25$, 95% CI [.05, .45], $p = .018$), a significant interaction between guidance and assessment time showed that the decrease in ES over time was greater in guided interventions ($\beta = -.02$, 95% CI [−.04, −.00], $p = .039$).

Are Digital Interventions Effective 'Beyond the Lab' in Routine Care Settings?

Of the included $k = 83$ studies, only $k = 21$ (25.30%) studies reported on the ES of digital interventions on depression in effectiveness settings. The ES of digital interventions versus all control conditions in these effectiveness studies was $g = .30$, 95% CI [.15, .45], $p < .001$; $I^2 = 85$, 95% CI [37, 100]; $\sigma^2_{within} < .001$, 95% CI [.000, .022], $\sigma^2_{between} = .095$, 95% CI [.042, .224] compared with the ES in efficacy trials ($g = .59$, 95% CI [.50, .69], $p < .001$; $I^2 = 81$, 95% CI [50, 100]; $\sigma^2_{within} < .001$, 95% CI [.000, .009], $\sigma^2_{between} = .115$, 95% CI [.072, .187]. Hence, the superiority of digital interventions over combined active and passive control conditions was demonstrated in both efficacy and effectiveness settings. However, the ES was significantly lower in effectiveness trials compared with efficacy trails ($\beta = -.30$, 95% CI [−.11, −.48], $p = .002$) explaining 13.5% of the between-study variance. For the forest plots for efficacy and effectiveness trials see Supplemental Appendices L and M in the online supplemental materials.

As results indicated a significant difference in ES between active and passive control conditions (with lower ES found for active control conditions) and ES in effectiveness settings was found to be significantly lower than in efficacy settings, we included both variables in metaregression to investigate the ES of digital interventions versus active control conditions in effectiveness settings. The results showed an average ES (intercept) of $g = .22$, 95% CI [.09, .35], $p = .002$; $I^2 = 79$, 95% CI [52, 100]; $\sigma^2_{within} < .001$, 95% CI [.000, .005], $\sigma^2_{between} = .093$, 95% CI [.062, .143] for digital interventions compared with active control conditions in effectiveness settings. The main effect of setting was $\beta = .21$, 95% CI [.04, .39], $p = .019$, indicating higher ES for digital interventions compared with active control conditions in efficacy settings compared with effectiveness settings. When controlling for the study setting the main effect of control type was nonsignificant with $\beta = .54$, 95% CI [−.52, 1.60], $p = .189$. The interaction between study setting and control type was also nonsignificant ($\beta = -.27$, 95% CI [−1.21, .66], $p = .445$).

To provide further details on the different active control conditions we ran subset analyses for each control type in effectiveness settings. Treatment as usual control conditions were most often used in effectiveness studies ($n = 15$), followed by attention control conditions ($n = 5$), wait-list control conditions ($n = 4$), and face-to-face control conditions ($n = 1$). The subset of WLC condition showed the highest average effect $g = .81$, 95% CI [−111, 2.74], $p = .161$; $I^2 = 89$, 95% CI [0, 100]; $\sigma^2_{within} < .001$, 95% CI [.000, 5.28], $\sigma^2_{between} = .379$, 95% CI [.000, 8.35], although nonsignificant. TAU control condition yielded a significant effect

favoring digital interventions $g = .30$, 95% CI [.19, .41], $p < .001$; $I^2 = 51$, 95% CI [0, 100]; $\sigma^2_{within} < .001$, 95% CI [.000, .034], $\sigma^2_{between} = .016$, 95% CI [.000, .061]. Interestingly, the comparison of digital interventions vs. attention control conditions in effectiveness settings showed a null finding of $g = -.01$, 95% CI [−.51, .49], $p = .939$. In the only study comparing a digital intervention against a face-to-face control condition in effectiveness settings, the difference was nonsignificant, $g = .01$, 95% CI [−.79, .76] (Wagner et al., 2014).

Finally, we investigated whether the benefits of guidance found in the combined efficacy and effectiveness settings persisted in the subset of effectiveness settings. As before, we found a nonsignificant benefit for technical guidance ($\beta = .13$, 95% CI [−.11, .36], $p = .272$) and a significant effect for human therapeutic guidance ($\beta = .37$, 95% CI [.19, .56], $p < .001$). For guided digital interventions compared with combined control conditions the overall ES was $g = .73$, 95% CI [.60, .85], $p < .001$). Testing for an interaction effect between study setting (efficacy vs. effectiveness) and guidance (UG vs GS) revealed a significant interaction ($\beta = .10$, 95% CI [.03, .17], $p = .014$, suggesting that guidance may be especially important in effectiveness settings.

Other Factors Moderating Outcomes

Participant Characteristics

Metaregression analysis revealed that digital interventions were equally effective in individuals with somatic comorbidities ($\beta = .05$, 95% CI [−.13, .23], $p = .551$). Similarly, gender (the percentage of women within a trial) had no impact on ES ($\beta = .03$, 95% CI [−.06, .11], $p = .517$). ES was not influenced by z-standardized age either ($\beta = -.05$, 95% CI [−.13, .24], $p = .176$). However, we found only sparse evidence assessing the efficacy of digital interventions for children and adolescents ($k = 4$). A subset analysis on these four studies yielded a nonsignificant effect of digital interventions ($g = .15$, 95% CI [−1.34, 1.63], $p = .708$; $I^2 = 94$, 95% CI [0, 100]; σ^2_{within} fixed to zero, $\sigma^2_{between} = .299$, 95% CI [.045, 5.734]. Refer to Appendix N and O in the online supplemental materials for the forest plots. Baseline depression severity significantly influenced ES (*z*-standardized: $\beta = .12$, 95% CI [.04, .20], $p = .005$; in PHQ: $\beta = .04$, 95% CI [.01, .07], $p = .005$), indicating individuals with higher depression symptom severity benefit more from digital interventions that individuals with lower baseline symptom severity.

Compliance

We operationalized intervention compliance in two ways: (a) the percentage of completers and (b) the average completion of modules in percentage. A total of 55 data points from 49 studies contained information on the percentage of completers, whereas there were 40 data points from 36 studies on the average completion of modules. The intercept-only model yielded an average completer rate of 53.49%, 95% CI [44.62%, 62.368%], $p < .001$; $I^2 = 65$, 95% CI [0, 100]; $\sigma^2_{within} < .001$, 95% CI [.000, .052], $\sigma^2_{between} = .046$, 95% CI [.000, .085] and an average module completion rate of 67.85%, 95% CI [59.00%, 76.07%], $p < .001$; $I^2 = 52$, 95% CI [0, 100]; $\sigma^2_{within} < .001$, 95% CI [.000, .049], $\sigma^2_{between} = .026$, 95% CI [.000, .059].

To quantify the influence of compliance on ES, we first calculated the ES of digital interventions in these two subsets of completers and module completion. The overall ES of digital interventions in the completer subset was $g = .65$, 95% CI [.53, .78], $p < .001$; $I^2 = 85$, 95% CI [0, 100]; $\sigma^2_{within} = .026$, 95% CI [.000, .190], $\sigma^2_{between} = .131$, 95% CI [.000, .251] and in the module completion subset $g = .50$, 95% CI [.37, .63], $p < .001$; $I^2 = 81$, 95% CI [0, 100]; $\sigma^2_{within} < .001$, 95% CI [.000, .137], $\sigma^2_{between} = .102$, 95% CI [.000, .204]. Investigating the influence of compliance on ES showed a strong influence in both subsets: the estimated increase in ES if all participants were completers was estimated at $\beta = .57$, 95% CI [.04, 1.10], $p = .037$, and the estimated increase in ES if, on average, 100% of the modules were completed was $\beta = .61$, 95% CI [−.05, 1.26], $p = .068$.

Given this strong influence of compliance on effectiveness, additional analyses were conducted to identify moderators of compliance. The average module completion rate in unguided interventions was 53.67%, 95% CI [34.00%, 73.35%], $p < .001$, 60.90%, 95% CI [40.67%, 81.14%], $p < .001$ in interventions with technical guidance and 76.31%, 95% CI [65.76%, 86.85%], $p < .001$ in interventions with therapeutic guidance. A comparison of module completion in guided vs. unguided interventions showed a significant effect of $\beta = 22.81\%$, 95% CI [5.18%, 40.43%], $p = .016$, and a nonsignificant effect for technical guidance compared with unguided interventions, $\beta = 7.73\%$, 95% CI [15.26%, 30.72%], $p = .474$.

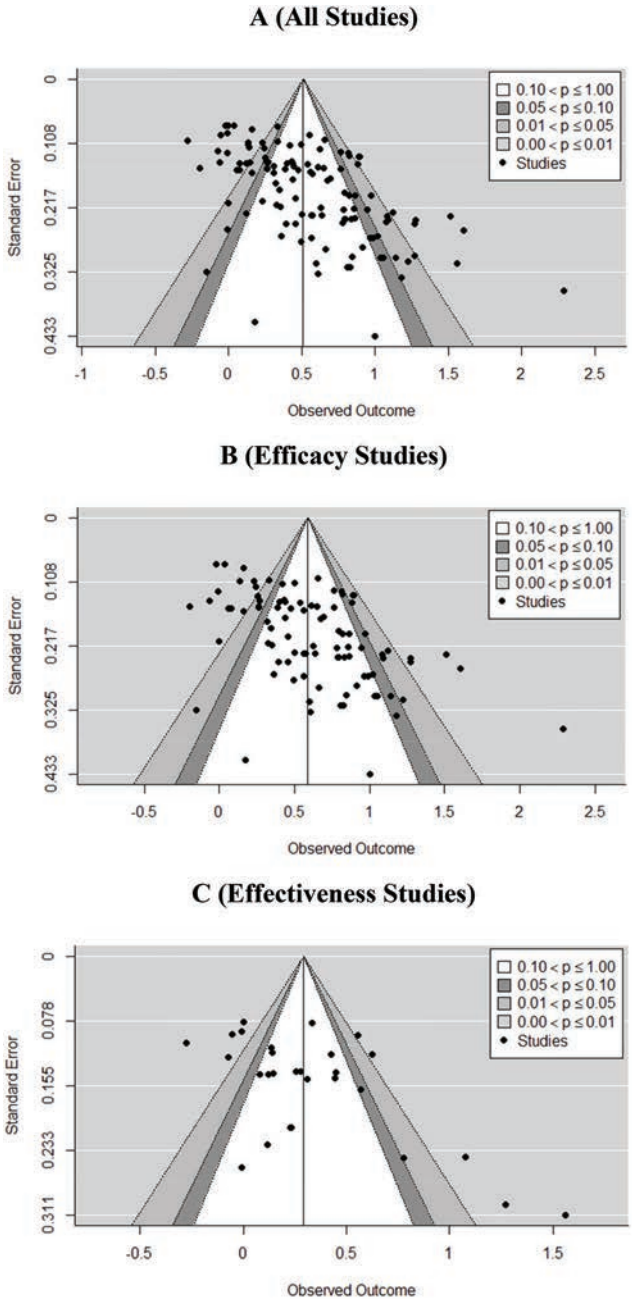
Similar differences across guidance formats were found for the percentage of completers. The percentage of completers was 38.11%, 95% CI [7.87%, 68.35%], $p = .022$ in unguided interventions, 50.30%, 95% CI [26.68%, 73.91%], $p = .001$ in interventions with technical guidance and 56.36%, 95% CI [47.95%, 64.76%], $p < .001$ in interventions with therapeutic guidance. However, there was no significant difference in percentage of completers when comparing guided interventions with unguided interventions ($\beta = 22.31\%$, 95% CI [−9.26%, 53.86%], $p = .141$) and interventions with technical guidance versus unguided interventions ($\beta = 9.03\%$, 95% CI [18. 44%, 36.50%], $p = .467$).

We found a significant difference in intervention compliance between efficacy and effectiveness settings. The percentage of completers in effectiveness settings was estimated at 25.22%, 95% CI [10.95%, 39.48%], $p = .004$; $I^2 = 48$, 95% CI [0, 82]; $\sigma^2_{within} = .027$, 95% CI [.000, .055], $\sigma^2_{between} < .001$, 95% CI [.000, .046], which was 35.67%, 95% CI [17.143%, 53.52%], $p < .001$ lower than in efficacy trials. The percentage of module completion in effectiveness settings was estimated at 53.61%, 95% CI [41.70%, 65.53%], $p < .001$; $I^2 = 40$, 95% CI [0, 100]; $\sigma^2_{within} < .001$, 95% CI [.000, .042], $\sigma^2_{between} = .018$, 95% CI [.000, .048], which was 21.01%, 95% CI [5.21%, 36.81%], $p = .012$, lower than in efficacy trials. Neither age nor gender significantly influenced compliance ($p > .05$). Temporal analyses found no significant change in treatment compliance (either in terms of average percentage of completers or average percentage of modules completed) over the last two decades.

Publication Year

Last, we explored whether the ES of digital interventions changed over time. Since there was only one study published in the first decade (Selmi et al., 1990), we focused on the last two

Figure 3
Funnel Plot to Assess for Publication Bias by Relating Effect Sizes to Standard Errors

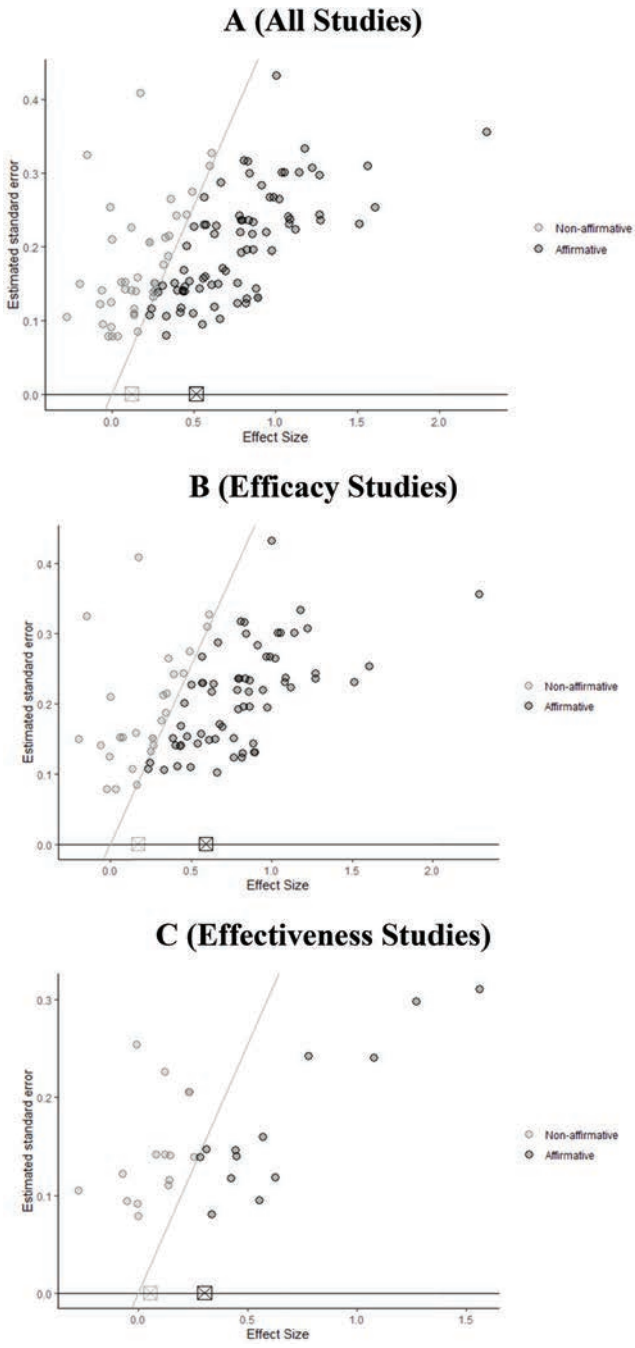


decades of studies to avoid bias caused by Selmi et al., 1990. We found no significant change in ES in the last 2 decades ($p > .05$).

Small Study Effects and Publication Bias

To investigate publication bias and small study effects, a funnel plot of the post effect sizes included in the present study was created (see Figure 3). The funnel plot clearly demonstrated an asymmetrical distribution of published effect sizes: studies with larger sample sizes (and thus lower standard error and higher precision) tended to find lower effect sizes, indicating that smaller studies finding low (or negative) ES may not have been published. This visual finding was further corroborated by the Egger's test: the modified Egger's regression model showed a significant effect of

Figure 4
Significance Funnel Plots for (A) All Studies, (B) Efficacy Studies, and (C) Effectiveness Studies



Note. Studies on the diagonal line have exactly $p = .05$. Gray square: worst-case estimate of effect size based only on nonsignificant studies. Black square: estimate of effect size for all studies.

Table 5
Publication Bias-Corrected ES Based on Increased Likelihood of Affirmative Results (η)

	All studies		Efficacy studies		Effectiveness studies	
Assumed η	ES	95% CI	ES	95% CI	ES	95% CI
1 (no publication bias)	0.53	[0.44, 0.62]	0.60	[0.49, 0.70]	0.30	[0.13, 0.48]
2	0.42	[0.33, 0.52]	0.50	[0.39, 0.62]	0.22	[0.07, 0.36]
3	0.37	[0.28, 0.46]	0.45	[0.33, 0.56]	0.18	[0.05, 0.30]
4	0.33	[0.24, 0.41]	0.41	[0.29, 0.52]	0.15	[0.04, 0.27]
5	0.30	[0.22, 0.38]	0.38	[0.27, 0.48]	0.14	[0.03, 0.25]
10	0.23	[0.16, 0.30]	0.30	[0.20, 0.40]	0.10	[0.01, 0.20]
15	0.21	[0.14, 0.27]	0.27	[0.18, 0.36]	0.09	[−0.00, 0.18]
20	0.19	[0.13, 0.26]	0.25	[0.16, 0.34]	0.08	[−0.01, 0.18]
30	0.18	[0.11, 0.24]	0.23	[0.13, 0.32]	0.08	[−0.02, 0.17]
50	0.16	[0.10, 0.23]	0.22	[0.13, 0.31]	0.07	[−0.02, 0.16]

Note. η = indicates the extent to which affirmative findings are more likely to be published; ES = effect size.

precision (β = −.29, 95% CI [−.07, −.51], p = .016). However, because effectiveness studies tend to have higher sample sizes, we tested efficacy and effectiveness studies separately. Interestingly, Egger's test was only significant in the efficacy studies subset (β = −.31, 95% CI [−.57, −.05], p = .029) and not in the effectiveness studies subset (β = −.12, 95% CI [−.47, .22], p = .272), indicating that bias may only be present in studies conducted in efficacy settings, but not those conducted in effectiveness studies. In addition to the influence of small study effects, we also investigated the differences between affirmative (k = 79) and nonaffirmative (k = 42) studies to detect potential publication bias. The significance funnel plot highlighted a substantial difference between ES across all studies (g = .52, 95% CI [.43, .60], p < .001) and the ES across only the nonaffirmative studies (g = .12, 95% CI [.06, .19], p < .001), indicating a possible influence of publication bias on the current findings (see Figure 4). However, affirmative studies would have needed to be 4.1-fold more likely to be published to move the lower CI of the ES below a clinically relevant effect of g = .24 (Cuijpers, Turner, et al., 2014), 9.25-fold more likely to move the ES itself to this threshold, and 23.8-fold more likely to move the lower CI to the "worst-case" ES of g = .12 (see ES of nonaffirmative studies). In a recent benchmark analysis (Mathur & VanderWeele, 2020), the empirical increased likelihood for affirmative results (η) based on 58 meta-analyses was estimated at η = 1.17 (.93 to 1.47) and the 95th quantiles of the distribution of the true η was estimated to be 3.51. Given these approximated benchmarks and that a η = 4.1 would have been needed to move the lower confidence interval and η = 9.25 to move the ES itself below clinical relevance in the present analysis, we conclude that the ES of digital interventions is likely to be clinically relevant, despite the present publication bias. For publication bias-corrected ES for different assumed η see Table 5.

Discussion

The Efficacy of Digital Interventions

The current study is the largest and most comprehensive meta-analysis conducted to-date assessing the efficacy of digital interventions for the treatment of depression across both active and inactive control conditions and in both efficacy and effectiveness settings. Overall, across 83 studies and 15,530 participants, we found a medium pooled effect size superiority of digital interventions across all control conditions (g = .52) with benefits sustained at follow-up.

An interesting point of comparison for our findings on digital interventions are effect sizes found in meta-analyses of face-to-face psychotherapy. In the largest and most-recent meta-analysis of psychotherapy for depression, Cuijpers et al. (2020) identified an overall effect size of g = .75 for face-to-face therapy compared with all control conditions (in contrast to g = .52 found for digital interventions in the current study), g = .91 when face-to-face psychotherapy was compared with waitlist control conditions (in contrast to g = .70 for digital interventions found in the current study) and g = .61 when face-to-face psychotherapy was compared with TAU (in contrast to g = .31 for digital interventions found in the current study).

The current review identified only three studies that directly compared digital interventions with face-to-face therapy. We found no significant difference in outcomes between the two conditions, supporting findings from Carlbring et al. (2018). However, unlike the study by Carlbring and colleagues, which mixed individual and group-based psychotherapy, our analysis was limited to individual therapy alone. It is important to note that these were highly controlled trials across multiple conditions and with low sample sizes, the majority of whom were self-referred. Moreover, participants needed to consent to both possible assignments of Internet or on-site care, likely leading to a highly selective subsample of depressed participants in need of mental health care. Based on these findings, and the notable lack of high-quality studies providing direct comparisons, we believe it is premature to conclude that digital interventions are as equally effective as face-to-face psychotherapy for the treatment of depression and mark this out as a critical area for future research.

The effect sizes found in the current meta-analysis varied greatly with respect to different forms of interventions (with larger effect sizes in interventions with a human support component), degree of standardization (with larger effect sizes in highly controlled efficacy studies), and populations (with insufficient evidence of efficacy for children and adolescents). While digitization has become a central concept in health policy worldwide to overcome existing gaps in the provision of mental health care (U.S. Food & Drug Administration., 2020; World Health Organization, 2020), the results of this meta-analysis suggest that the evidence should be evaluated carefully for individual interventions and within individual settings.

Finally, despite the comprehensive search strategy used in the current review, we found no studies that directly compared digital interventions with pharmacotherapy. Given the large body of research comparing psychotherapy with medication for the treatment of depression, we believe that such comparisons are critical if digital interventions are to be considered as part of the care pathway in clinical settings. In line with this, we would also benefit from an understanding of how outcomes evolve over time between the different treatment modalities. Similar to the evidence suggesting that psychotherapy may be more effective in the long-term than antidepressant medication for mild-to-moderate depression (Karyotaki et al., 2016), a better understanding of where digital interventions fit into this picture is an important area for future research in the field.

The Role of Human Support

In contrast to recent studies suggesting that the addition of human support may have no influence on outcomes in digital interventions (Shim et al., 2017), the current meta-analysis found that interventions with therapeutic guidance had a higher overall effect size (g = .63) than interventions with technical guidance (g = .46) and led to significantly better outcomes than unguided interventions (g = .34). Our results corroborate the findings by Richards and Richardson (2012), though the current meta-analysis included a substantially larger number of trials (83 vs. 24 RCTs) from almost a decade more of research.

The increased effect size found in guided interventions may be explained by the increase in treatment compliance. According to the Supportive Accountability model (Mohr et al., 2011), human support increases compliance with an intervention due to accountability to a coach who is seen as trustworthy, benevolent and having expertise. Indeed, in our analysis we found a significant influence of guidance on treatment compliance. On average, across all studies, participants completed 67.9% of the intervention. Yet, participants who received therapeutic guidance completed on average 76.3% of the intervention. In contrast, those who received technical guidance completed an average of 60.9% and participants who received no human support only completed an average of 53.7% of the intervention.

Treatment compliance is a key factor in moderating outcomes in psychotherapy (Hansen et al., 2006). The current study found a strong dose–response relationship between the number of modules completed and outcomes. Importantly, we found that completing the full intervention had the largest influence on reducing depressive symptoms of any moderator variable in our model (β = .501). Yet, despite this, on average, only 53.5% of participants completed the full intervention across studies. Such findings stand in stark contrast with a meta-analysis of face-to-face therapy where the average percentage of completers was 84.7% (van Ballegooijen et al., 2014).

The higher effect sizes found in studies providing therapeutic guidance compared with technical guidance suggests that the role of human support in digital interventions may extend beyond simply facilitating compliance. As in face-to-face therapy (Henry et al., 1990; Norcross, 2010), several therapist behaviors have been associated with positive outcomes in digital interventions. For instance, Holländare et al. (2016), revealed that interpreting and normalizing patient interactions with the intervention (affirming), praising past and planned behaviors (encouraging), and mentioning personal examples from their own lives (self-disclosure) were all shown to significantly influence treatment outcomes in Internet-based CBT.

Yet, despite the influence of guidance on outcomes, we found no relationship between the amount of guidance provided and effect size. We also found no relationship between the qualification and profession of the person providing guidance on outcomes. One explanation for this may be the highly standardized nature of digital interventions. In contrast to face-to-face therapy, digital interventions are largely designed as self-help treatments, where the role of the therapist is to provide clarification and reinforcement of preexisting therapeutic content (Ebert et al., 2018). As such, the experience and expertise of a trained psychotherapist may be less relevant for many individuals. Given the implications these findings have on the implementation and scalability of digital interventions in clinical settings, we would benefit from a deeper understanding of the role of human guidance, in particular for whom guidance is necessary and the optimal amount of guidance needed to maximize outcomes.

Beyond the Lab: From Efficacy to Effectiveness

Whether the efficacy of digital interventions found in developer-led trials can be transferred into clinical settings is a critical question if digital interventions are to be offered to patients as an alternative to face-to-face therapy. In the current study, we found a small-to-medium positive effect size (g = .30) for digital interventions in effectiveness settings. Furthermore, we found that digital interventions were significantly more effective than TAU in routine care settings (g = .30), answering an open research question that has previously generated significant debate when posed at the individual study level (Gilbody et al., 2015a, 2015b).

Nonetheless, we found that effect sizes were significantly lower for effectiveness studies than in efficacy trials (g = .59). This may be explained by the lower compliance found in effectiveness trials. On average, participants in effectiveness studies completed 53.6% of the intervention (compared with 74.6% in efficacy trials) and only 25.2% of participants completed the full intervention (compared with 60.9% in efficacy trials). The differences here may be attributable to the different study participants in the two designs: in efficacy trials, participants typically self-select, are more motivated to comply with treatment, and often receive remuneration for participation. In contrast, participants in effectiveness trials may have more severe or complex conditions and may also be unwilling to accept psychological therapy without face-to-face contact (Knowles et al., 2015).

Overall, our findings from effectiveness studies suggest that digital interventions may have a valuable role to play as part of the treatment offering in routine care, especially when accompanied by some sort of human guidance. A small but growing number of pragmatic trials of digital interventions in clinical settings provide further evidence of this (Titov et al., 2018). The U.K.'s Improving Access to Psychological Therapies (IAPT) program is one successful case in point, treating more than 500,000 people each year within the public health care system (Clark, 2018). As part of a "stepped care" offering, IAPT first offers digital interventions to individuals with mild-to-moderate depression and/or anxiety (low-intensity interventions) and face-to-face therapy (high-intensity interventions) to those with more severe or complex symptomatology. With regular outcome monitoring (after every session), care

pathways can then be updated during treatment to improve overall outcomes. In this way, evidence-based treatment can be scaled to match individual needs as well as optimize service capacity. At the same time, unguided self-help interventions may have a valuable role to play as an alternative to 'watchful waiting' in mild depression (Cuijpers, Quero, Dowrick, et al., 2019; Karyotaki et al., 2021) or in the prevention of major depression for those with subthreshold depression (van Zoonen et al., 2014).

For digital interventions to really scale to meet the needs of large populations, a number of challenges still need to be addr -essed, however. Among these are concerns over the perceived lack of clinical effectiveness of digital interventions, the significantly higher preference for face-to-face or blended therapy and the belief that current care systems are not setup to properly integrate digital modalities (Topooco et al., 2017). The evidence base for digital interventions in low-income settings and diverse cultures is also woefully lacking. In the current analysis, we found only three studies conducted in Asia, one study conducted in South America and no studies in Africa. Depression is a global public health problem with similar prevalence rates between low-income and high-income countries, yet a significantly lower proportion of people in low-income countries currently receive care due to lack of funding and trained health care providers (Cuijpers, Quero, Dowrick, et al., 2019).

Other Factors Moderating Outcomes

The current meta-analysis investigated the influence of a number of participant characteristics on outcomes, including gender, age, somatic comorbidity and baseline depression severity. In line with previous studies (Cuijpers et al., 2014; Donker, Batterham, et al., 2013), we found no significant difference in outcomes between males and females. Regarding age, we found a significantly lower effect size for children and adolescents than for adults (g = .15 vs. g = .53). The average effect size found in the current analysis was lower than has been found in prior meta-analyses on digital interventions for depression in youth (Ebert et al., 2015; Garrido et al., 2019). However, these meta-analyses have also included young adults (most often up to the age of 25 years), which may have obscured the "real" effect sizes for children and adolescents. Indeed, as recent meta-analyses have demonstrated, there is a clear tendency for effect sizes of psychotherapeutic interventions to be substantially lower in younger children with depression, whether delivered face-to-face (Cuijpers, et al., 2020a) or by digital means (Domhardt et al., 2020). Notwithstanding the above, we found only four studies targeting children and adolescents (Gladstone et al., 2018; Ip et al., 2016; Smith et al., 2015; Wright et al., 2017). Given the growing prevalence of childhood and adolescent depression (Mojtabai et al., 2016), the field would benefit from further research on digital interventions targeting these age groups with a specific focus on what factors may lead to improved outcomes (Domhardt, Schröder, et al., 2021).

We found no difference in the effectiveness of digital interventions in patients with comorbid somatic conditions compared with those without, reflecting what has been found for psychotherapies in general (Cuijpers et al., 2018). This is promising given the increased prevalence of depressive symptoms in patients with chronic medical conditions and the manifold negative consequences of physical and mental comorbidity (Anderson et al., 2001; Egede & Ellis, 2010). Furthermore, as antidepressant treatment may bring the possibility of adverse drug interactions creating reluctance in patients and physicians to initiate new pharmacological treatment (Boele et al., 2018), our findings suggest that digital interventions may offer a promising alternative for patients experiencing comorbid depressive symptoms that may help overcome the separation of physical and mental health care (Narasimhan et al., 2019; Shrank et al., 2019).

Whether digital interventions are suitable for individuals of all levels of depression also has substantial clinical implications. Despite the fact that the majority of trials involving digital interventions exclude participants with severe levels of depression and most clinical guidelines do not recommend Internet-based therapy as a first-line treatment for individuals with severe depression (NICE, 2017; "Practice Guideline for the Treatment of Patients with Major Depressive Disorder (Revision), American Psychiatric Association," 2000), we found a greater effect size for participants with higher pretreatment depression severity than those with lower baseline symptom scores. Similar findings have been reported elsewhere (Karyotaki, Ebert, et al., 2018; Williams & Andrews, 2013) and may simply reflect the fact that these participants have greater room for improvement. However, it is worth noting that only 1% of studies in the present analysis involved participants with severe levels of depression. Furthermore, more important than efficacy may be the question of whether digital interventions are safe for patients with severe mental disorders. Although two IPD meta-analyses have highlighted a low risk of deterioration of Internet-based interventions when compared with waitlist and TAU control conditions (Ebert et al., 2016; Karyotaki, Kemmeren, et al., 2018), we do not yet know whether Internet-based interventions are as safe as on-site treatment with regard to serious adverse events such as need for hospitalization and, particularly, suicide that occur relatively often in patients with severe depression (Sander, Gerhardinger, et al., 2020).

Finally, the current study assessed whether smartphone-based interventions are effective in the treatment of depressive symptoms. Here, we found an overall effect size of g = .40 compared with all control conditions, which was not significantly different to outcomes for computer- or Internet-based interventions, suggesting smartphone apps may be a viable modality for the treatment of depression in individuals with mild-to-moderate symptoms of depression. Although our results appear similar to those found in other meta-analyses on smartphone apps for mental health (Firth, Torous, Nicholas, Carney, Rosenbaum, et al., 2017; Weisel et al., 2019), it must be considered that only one trial in our analysis demonstrated the efficacy of an intervention that could be accessed only on a smartphone (Guo et al., 2020). Furthermore, we found only four RCTs of smartphone-based interventions that met our inclusion criteria, echoing the concerns from a number of researchers on the dearth of evidence and high dropout rates in trials conducted for smartphone-apps targeting depressive symptoms (Baumel et al., 2019; Larsen et al., 2019; Torous, Lipschitz, et al., 2020). Smartphone-based apps may offer a number of potential advantages over computer-based interventions, most notably their ability to gather data and deliver interventions in real-time and in situ (Torous et al., 2019). Given their rapid adoption worldwide, they may also be particularly well-suited to providing large scale self-help preventative interventions and treatment for individuals

with subclinical depression. We thus highlight this as a promising area for future research.

Strengths

To the best of our knowledge, this meta-analysis is the first to directly compare effect sizes across control conditions in effectiveness settings, allowing us to answer the question as to whether digital interventions lead to superior outcomes when compared with the usual care provided in routine health care settings. Unlike many of the existing meta-analyses of digital interventions for depression that have been limited to studies involving adult populations (aged 18–65), only one therapeutic approach (typically CBT), or one treatment modality (e.g., smartphones), our analysis included participants of all ages and therapeutic approaches and across all treatment modalities, allowing us to comment on important differences in outcomes related to these factors. Finally, using a multilevel metaregression model in our analysis, we were able to include outcomes from multiple measures and time points included in a study providing a more accurate analysis of outcomes and additional insight into potential changes in effect size over time.

Limitations

Several limitations of the current meta-analysis should be considered. First, we observed substantial heterogeneity (I^2 = 84%). However, with the predictors "control type" (active vs. passive) and "study setting" (effectiveness vs. efficacy) we identified two major sources of between-study variance explaining 22.4% and 13.5% of the between-study variance, respectively.

Second, our search strategy was limited to published peer-reviewed studies and thus excluded gray literature. As studies with negative or inconclusive results are less likely to be published this may have led to an overestimation of effect sizes (Rothstein et al., 2005). Although the influence of including gray literature on pooled ES estimates may be less than expected (Schmucker et al., 2017), our analyses did reveal significant small study effects, suggesting an influence of publication bias on the current findings. Such bias may also account for a proportion of the difference in effect sizes between efficacy and effectiveness trials, where efficacy trials appeared to have publication bias and effectiveness trials did not. Notwithstanding, even with an assumed increased likelihood of up to 4-fold the number of affirmative studies being published over nonaffirmative studies, our findings indicate a clinically relevant ES ($g > .24$, 95% CI) for digital interventions versus combined control conditions.

Third, 95% of included studies were conducted across Europe, Australasia, and the United States; we only found one study published in the last 30 years conducted in South America and none in Africa, limiting the generalizability of our findings to these continents where populations and health care systems may differ considerably.

Fourth, the operationalization of control conditions (e.g., WLC and TAU) may have differed between studies, causing 'methodological heterogeneity' when pooling effect sizes. As previous research has demonstrated that control conditions may vary across settings and between countries (Cuijpers, Quero, Papola et al., 2019), caution should be exercised when interpreting these results.

Fifth, we based our classification of self-guided/unguided, and guided interventions with either therapeutic or technical support on the a priori intervention design and operationalization stated in the publications of the primary studies. However, the actual implementation and uptake of guidance during the process of carrying out of each study might have differed to what was intended. Thus, to fully understand the impact of the actual implementation of guidance, precise and detailed information on the actual support delivered and the specific uptake from patients would be necessary.

Finally, it is important to note that our analysis was carried out at the study level, (i.e., using aggregate data from groups), thereby preventing us from making causal inferences about the role of the included moderators. This is particularly relevant for patient level moderators where our results should be interpreted with caution due to possible power limitations. Meta-analyses based on individual participant data (IPDMA) are a more appropriate method to identify moderators in patient characteristics compared with metaregression as they enable the standardization of analyses across studies (thereby minimizing heterogeneity) and provide greater statistical power to identify potential moderators (Cooper & Patall, 2009; Furukawa et al., 2021; Karyotaki et al., 2021). Furthermore, IPDMA offer several other advantages like the possibility to account for missing data at the individual level, allow for the verification of the original study publication information with the actual data sets and facilitate the inclusion of study participants who were initially excluded in the analyses of primary studies (Riley et al., 2010). To facilitate the IPDMA approach, it is also of paramount importance that future research collects and reports on common outcome measures and fine-grained data related to patient characteristics, especially on groups for whom digital interventions may hold significant potential to reduce existing gaps in care (for example, low-income clients, clients living in rural areas, or ethnic minority clients (Mohr et al., 2014; Muñoz et al., 2018). The recommendations provided by the International Consortium for Health Outcomes Measurement (ICHOM) offer a promising framework here. The ICHOM proposes a standard set of outcome measures for anxiety and depression relevant across countries and cultures (Obbarius et al., 2017). These measures include demographic factors related to age, sex, gender identity, socioeconomic status, ethnicity, marginalized group status and living situation (Krause et al., 2021; Obbarius et al., 2017). With such standards in place, researchers and policymakers will be better positioned to compare the effectiveness of different care systems and models of care at the same time as having greater transparency into the quality of care across different populations and intervention settings.

Future Directions

Despite the demonstrated efficacy and effectiveness of digital interventions, we would like to emphasize that the effect sizes found were modest, especially outside of highly controlled settings. Moreover, similar to findings in face-to-face psychotherapy (Cristea et al., 2017; Johnsen & Friborg, 2015), our moderator analyses revealed that there has been no increase in effect size for digital interventions over the past 2 decades. For this to change in the decades that follow, we mark out three areas in particular for future research: (a) addressing the problem of compliance in digital interventions; (b) leveraging digital interventions for a deeper

understanding of how therapy works; and (c) the development of personalized models of depression and tailored interventions in precision medicine.

Putting the "Science of Attrition" Back on the Agenda

One of the key findings in our review was the high levels of noncompliance found in digital interventions, especially in clinical settings and in unguided interventions. It has long been known that compliance is a challenge in digital interventions (Christensen et al., 2009; Donkin et al., 2011; Eysenbach, 2005)—and indeed compliance was the largest predictor of outcomes in our analysis—yet, we found no difference in average compliance in the past 20 years. Given the significant role that compliance plays in mediating outcomes, we highlight this as a critical area for future research, echoing the need for what has been referred to as a "science of attrition" (Eysenbach, 2005).

Three areas of research hold promise here. First, the role of guidance. It is now well established that compliance in guided interventions is significantly higher than in unguided interventions. However, less is known as to *why* guided interventions lead to increased compliance and what the optimal amount (frequency and duration), type of focus (therapeutic vs. technical), and delivery channels (e.g., telephone, emails) might be. We would also benefit from a deeper understanding of which patients may be best suited to unguided interventions and who may need human support or face-to-face therapy as well as the mechanisms operating here and how they may be influenced. One promising approach here are network meta-analyses (NMAs) using individual participant data (IPD; Furukawa et al., 2021; Karyotaki et al., 2021). Unlike RCTs, which are typically underpowered to answer questions related to 'what works best for whom', IPD NMAs can combine multiple comparisons in a single analysis, using both direct and indirect evidence (Mavridis et al., 2015). As such, they have greater statistical power when examining patient level characteristics that may moderate outcomes across different interventions.

Second, patients may also develop an alliance with the program itself, not just the guiding therapist, which has implications for intervention design (Berger, 2017). For example, interventions that are personalized to individuals based on their presenting symptoms or previous interactions with the program may better reflect the element of responsiveness in therapeutic alliance known to influence outcomes (Kramer & Stiles, 2015; Stiles et al., 1998). Several studies have already demonstrated the role of persuasive design elements (e.g., design and content personalization; Baumeister et al., 2019; Kelders et al., 2012, 2015) and automated communications (e.g., email, text messages or chatbots; Bendig et al., 2019; Kelders et al., 2015; Titov et al., 2013) on increasing compliance. As technological capabilities develop and new modalities evolve, we would benefit from further research into design factors influencing compliance, especially in unguided interventions where compliance outside controlled settings is typically very low and thus the onus of maintaining patient engagement weighs more heavily on the intervention itself (Baumel et al., 2019).

Third, as the old adage goes "if you cannot measure it, you cannot manage it." In our review, only 36 of 83 studies (43%) provided measures of average treatment compliance and definitions of compliance varied widely. Some studies operationalized compliance as the average number of modules completed, while others defined it as proportion of participants completing the full intervention or a certain percentage of it. To complicate things further, module completion may only reflect one aspect of compliance. For example, frequency of logins, time spent interacting with the intervention and homework completion are all aspects of engagement that may influence outcomes but are not captured by module completion alone (Donkin et al., 2011; Enrique et al., 2019). Indeed, research has shown that effective usage patterns may vary between individuals (Sieverink et al., 2017) and that some individuals may not need to complete the full intervention to benefit from it (Christensen & Mackinnon, 2006). Future research may thus benefit from moving away from blunt instruments that reduce compliance to single dimensions and binary measures, toward more sophisticated, composite measures that better reflect the complexity of the way humans interact with digital applications. For example, a recent study employing machine learning models across a number of different interaction types was able to identify different subtypes of user engagement that predicted outcomes early on in the intervention (Chien et al., 2020). These insights may then be used to tailor interventions during treatment to maximize outcomes.

The Development of Mechanistically Driven Interventions

Even when participants do fully comply with the intervention, a significant proportion will still fail to experience any meaningful decrease in symptoms of depression (Andrews et al., 2000, 2004). To address this so-called "quality gap" it is time for us to move beyond a research agenda that has been predominantly focused on demonstrating *that* therapies work to one focused on understanding *how* therapies work (Cuijpers, 2016b). The majority of studies have compared outcomes between two groups of individuals in different conditions and proposed mechanisms of change based on the underlying differences found (Cuijpers, Reijnders, et al., 2019; Holmes et al., 2018). However, these types of studies are limited in their explanatory power as they can only provide correlational evidence for the purported mechanisms, not causal. To understand the causal mechanisms underlying change in psychotherapy, we need new experimental designs aimed at identifying the intervention components and mediators that make up the active ingredients of psychotherapy (Domhardt, Steubl, et al., 2021). Mediators can be seen as a way to operationalize, and thus reveal, potential mechanisms: the actual steps or processes through which therapy unfolds and produces the change (Kazdin, 2007). Understanding the mediators and mechanisms underlying change in psychotherapy is critical if we want to develop treatment strategies that directly target these mechanisms and remove redundant strategies (Furukawa et al., 2021; Holmes et al., 2018).

Digital interventions could provide researchers with a powerful experimental paradigm for the identification of mediators and mechanisms of change that overcomes some of the challenges with existing research on face-to-face therapies. First, the ability to target large sample sizes with the same intervention enables researchers to conduct trials that are sufficiently powered to detect the small effect sizes likely in studies on individual components and mediators of change (Domhardt, Steubl, et al., 2021). Second, the potential to deliver highly standardized digital interventions makes it easier to manipulate individual mediators while controlling for others (Domhardt, Cuijpers, et al., 2021; Furukawa et al., 2021). As such, it may limit the high levels of heterogeneity that have plagued psychotherapy research for decades. Third, the

ability to gather granular data relating to both the timing and amount of interaction with specific components of an intervention enable the temporal and gradient requirements of research on mediators (Kazdin, 2007).

Personalized Interventions for the Treatment of Depression

Digital interventions may also offer a unique platform to provide personalized treatment approaches that have simply not been possible until now. For a long time, mental disorders have been conceptualized using diagnostic categories, where disorders are defined based on a set of symptoms purported to derive from the disorder. However, mental disorders are more complex than this, evolving on multiple levels of action, from molecules to cells and circuits, to cognitions, emotions and behaviors, and interacting with social and physical environmental factors (Huys et al., 2016). As a result, there is a substantial degree of heterogeneity in symptoms between people diagnosed with the same disorder (Cramer et al., 2010); calling into question the validity of traditional psychiatric diagnoses (Maj et al., 2020).

The rapidly evolving field of computational psychiatry may provide novel methodological and epistemological approaches to address the limitations of the categorical nosology and lead to new insights for the personalization of treatments (Huys et al., 2016). Computational psychiatry integrates multiple levels and types of computation with multiple types of data to enhance the etiology, prediction, and treatment of mental disorders (Huys et al., 2021). As an increasing number of digital interventions are delivered via smartphones, they may constitute a central catalyst for computational psychiatry and provide an important role in capturing several units of analysis that have been extremely difficult to capture until now, most notably the behavioral, physiological, and self-report dimensions (Torous et al., 2017). For example, with the passive collection of smartphone sensor data, such as GPS for location tracking, microphone for vocal markers, and text and call logs for identifying social interactions, smartphones can capture a plethora of data related to an individual's behavioral patterns. Combined with physiological data from wearable devices, (e.g., sleep duration or heart rate variation (HRV) as a measure of stress), we can derive "digital phenotypes" (Montag et al., 2020; Onnela & Rauch, 2016) to aid the understanding of the causal factors in depression at both the inter- and intraindividual level. Such high-resolution and large-scale data can then be analyzed by advanced computational approaches. Although the research field is still nascent here, studies have already demonstrated relationships between GPS, HRV, calls and SMS logs, microphone and app usage, and depressive symptoms across clinical and nonclinical populations (Moshe et al., 2021; Rohani et al., 2018; Saeb et al., 2015, 2016). With access to moment-by-moment changes in an individual's psychological, behavioral, and physiological states, digital interventions thus have the potential to evolve into real-time adaptive interventions that can predict, prevent and treat disorders such as depression with mechanistically driven interventions personalized to the individual and delivered at the critical time to maximize outcomes.

Conclusions

The current meta-analysis provided evidence for the efficacy of digital interventions for the treatment of depression for a variety of populations. Furthermore, it demonstrated the superiority of digital interventions compared with treatment-as-usual in clinical settings when accompanied by human guidance. However, effect sizes are modest and compliance with digital interventions outside of highly controlled settings remains a significant challenge. For this to change in the decades that follow, researchers will need to adopt a research agenda focused on understanding how and for whom digital interventions work, rather than simply that they work, as well as how to successfully disseminate digital interventions beyond the lab in routine care settings.

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