Digital interventions for common mental disorders across the lifespan: Exploring active ingredients and mechanisms of change

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Part V. Mediators and mechanisms of change in digital interventions

8. * **Domhardt, M.**, Lutsch, A., Sander, L. B., Paganini, S., Spanhel, K., Ebert, D. D., Terhorst, Y., & Baumeister, H. (2023). Mediators of digital depression prevention in patients with chronic back pain: Findings from a multicenter randomized clinical trial. *Journal of Consulting and Clinical Psychology*. Advance online publication. https://doi.org/10.1037/ccp0000808

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11. * **Domhardt, M.**, Steubl, L., Boettcher, J., Buntrock, C., Karyotaki, E., Ebert, D. D., Cuijpers, P., & Baumeister, H. (2021). Mediators and mechanisms of change in internet- and mobile-based interventions for depression: A systematic review. *Clinical Psychology Review, 83*, 101953. https://doi.org/10.1016/j.cpr.2020.101953

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Abstract

Common mental disorders (CMD), such as depression and anxiety, are among the main contributors to the global burden of disease across age groups. Although a range of evidence-based psychotherapeutic interventions for these prevalent disorders exist, many patients receive no empirically-supported psychotherapeutic intervention due to the unavailability of mental health care services and other significant structural and individual barriers to treatment. Digital mental health interventions might represent an important approach to overcome this treatment gap and extend evidence-based psychotherapeutic service provisions, given some specific features like delivery independent from space and time, potential cost-effectiveness, scalability as well as possible anonymity. While the efficacy and effectiveness of digital interventions for most CMD in different age groups are established by dozens of randomized controlled trials (RCT) by now, comprehensive knowledge on the active ingredients and mechanisms of change in these interventions is still lacking. Insights on the active ingredients, mediators and working mechanisms is of high scientific and clinical relevance though, as it can inform the empirically-supported advancement of interventions and clinical practices, striving for augmented and efficient interventions with better treatment outcomes. As such, the overarching aim of this dissertation is to contribute to the knowledge on the active ingredients and processes of change in digital interventions for CMD across the lifespan, enhancing our understandings *whereby* and *how* these interventions work. To this end, a series of studies building on different methodologies were conducted, in order to meet the specific research questions at hand – with a particular focus on systematic reviews and meta-analyses of RCTs, providing the most comprehensive and best-available evidence. In specific, part I of this dissertation describes the systematic evaluation of the efficacy, effectiveness and quality of internet- and mobile-based interventions for different CMD across age groups with limited evidence so far (Chapters 1-4). These chapters contribute to the evaluation of the efficacy and effectiveness of digital interventions, since the establishment *that* these interventions work is a fundamental prerequisite for all subsequent research on change mechanisms. Part II designates a conceptual and integrative psychological model of the mechanisms of change in digital interventions for depression as a principal framework for (digitalized) research on psychotherapy processes (Chapter 5). In part III, the novel possibilities as well as the challenges of digitalized approaches to psychotherapy process research are outlined and discussed in a perspective paper (Chapter 6). Part IV describes the results of a systematic review and meta-analysis on the incremental effects of distinct intervention components of digital interventions for anxiety disorders in adults (Chapter 7). Part V can be conceived as the heart of this dissertation and is dedicated to

the mediators and mechanisms of change in digital interventions in four different settings: for the prevention of depression in patients with chronic back pain (Chapter 8), for several CMD in youth (Chapter 9), as well as for the psychological treatment of anxiety (Chapter 10) and depression (Chapter 11) in adults. These studies rely on three different methodologies, namely a secondary analysis of a multicenter RCT, two systematic reviews and a meta-analytic structural equation modeling approach. Overall, the results of this dissertation highlight that: (a) Digital interventions are effective for a range of CMD across the lifespan, with a robust trend of smaller effect sizes in unguided interventions (compared to guided interventions) and in interventions for younger age groups (i.e., adults > adolescents > children). (b) Uncertainties exist around the efficacy of mobile-based interventions. (c) A range of intervention components contribute to the efficacy of internet-based interventions, with an overarching importance of human guidance and modules that support the active coping of patients. (d) The qualification of e-coaches, the respective theoretical background and the disorder-specificity of interventions may not make a difference for the efficacy in anxiety disorders, as suggested by further meta-analytical evaluations. (e) A variety of distinct mediators transmit the efficacy of interventions, with cognitive factors appearing to be of particular relevance in depression and anxiety disorders. (f) Across studies, the best established, significant mediators are acceptance, mindfulness, self-efficacy, reductions in dysfunctional cognitions, perceived control and mastery, as well as emotion regulation particularly in youth. Finally, in part VI, the findings of this dissertation are integrated and discussed. Furthermore, implications for future research and methodological recommendations for forthcoming studies with more pertinent designs, allowing for inferences with higher causal certainty, are provided.

Zusammenfassung

Depression und Angststörungen gehören über alle Altersgruppen hinweg zu den häufigsten psychischen Störungen und tragen substantiell zur weltweiten Krankheitslast bei. Obgleich eine Reihe von evidenz-basierten psychotherapeutischen Interventionen für diese prävalenten Erkrankungen vorliegen, erhält eine Vielzahl von Patient:innen keine empirisch-fundierte Intervention aufgrund nur unzureichend zur Verfügung stehender psychotherapeutischer Versorgungsangebote sowie weiterer bedeutender struktureller und individueller Barrieren, welche einer Behandlung entgegenstehen. Digitale psychotherapeutische Interventionen könnten einen bedeutsamen Beitrag zur Überwindung dieser Versorgungslücke leisten und zu einer Ausweitung psychotherapeutischer Behandlungsangebote führen. Dabei dürften manche

ihrer spezifischen Eigenschaften zum Tragen kommen, wie etwa die Nutzungsmöglichkeit rund um die Uhr losgelöst von räumlichen Beschränkungen, der potentiellen Kosten-Effektivität, Skalierbarkeit sowie möglichen Anonymität in der Umsetzung. Wenngleich die Wirksamkeit digitaler psychotherapeutischer Interventionen für die meisten häufigen psychischen Störungen in verschiedenen Altersgruppen durch zahlreiche randomisiert-kontrollierte Studien (RCT) zwischenzeitlich als gut belegt anzusehen ist, besteht immer noch ein Mangel an fundiertem Wissen über deren Wirkfaktoren und Veränderungsmechanismen. Ein umfassendes und vertieftes Verständnis über die therapeutisch-relevanten Wirkfaktoren, Mediatoren und spezifischen Wirkungsweisen wäre jedoch von hoher wissenschaftlicher und klinischer Bedeutung, da diese Erkenntnisse eine empirisch-begründete Weiterentwicklung der Interventionen und klinischen Praxis ermöglichen würden. Darüber könnte ein wichtiger Beitrag zu optimierten und effizienteren Interventionen mit verbesserten Behandlungsergebnissen geleistet werden. Das übergeordnete Ziel dieser Dissertation besteht dementsprechend darin, zu einem erweiterten und vertieften empirisch-begründeten Wissen über die therapeutisch-aktiven Wirkfaktoren und Veränderungsmechanismen digitaler Interventionen für häufige psychische Erkrankungen über die Lebensspanne beizutragen, und damit unser Verständnis zu verbessern, *wodurch* und *auf welche Weisen* diese Interventionen wirken. Um dieses übergeordnete Ziel zu erreichen und um die jeweiligen spezifischen Forschungsfragen der einzelnen Untersuchungen so gut wie möglich beantworten zu können, wurde eine Reihe von Studien mit unterschiedlicher Methodologie durchgeführt – mit einem besonderen Schwerpunkt auf systematischen Übersichtsarbeiten und Meta-Analysen von RCTs, da diese die umfassendste und aussagekräftigste Evidenz aufbereiten und erbringen können. Im einzelnen widmet sich der erste Teil dieser Dissertation der systematischen Evaluation der Wirksamkeit und Qualität von Internet- und mobile-basierten Interventionen (IMIs) für verschiedene häufige psychische Störungen in unterschiedlichen Altersgruppen für welche bislang nur eine eingeschränkte empirische Evidenz vorgelegen hat (Kapitel 1-4). Diese vier Veröffentlichungen tragen damit grundlegend zur Evaluation der Wirksamkeit unter Labor- und Routine-Bedingungen bei, da der Nachweis *dass* diese Interventionen wirksam sind als eine notwendige Vorbedingung für nachfolgende Forschung über deren Wirkungsweisen angesehen werden kann. Der zweite Teil befasst sich mit der Entwicklung eines konzeptuellen und integrativen psychologischen Models über die Veränderungsmechanismen digitaler Interventionen für depressive Störungen als Rahmenwerk für die (digitalisierte) Psychotherapieprozessforschung (Kapitel 5). Im dritten Teil der Arbeit wird den Chancen und Grenzen von digitalisierten Ansätzen im Feld der Psychotherapieprozessforschung

nachgegangen und diese in einem Perspektivenartikel kritisch diskutiert (Kapitel 6). Der vierte Teil beschreibt die Ergebnisse einer Meta-Analyse zu den Effekten einzelner Interventionskomponenten von IMIs gegen Angststörungen (Kapitel 7). Der fünfte Teil – welcher als Herzstück dieser Dissertation angesehen werden kann – widmet sich den Mediatoren und Veränderungsmechanismen digitaler Interventionen in vier verschiedenen Anwendungsbereichen: für die Prävention von depressiven Störungen bei Patient:innen mit chronischen Rückenschmerzen (Kapitel 8), für eine Reihe von häufigen psychischen Störungen im Kindes- und Jugendalter (Kapitel 9), sowie bei der psychotherapeutischen Behandlung von Angststörungen (Kapitel 10) und Depression (Kapitel 11) im Erwachsenenalter. Dabei kommen drei verschiedene Studiendesigns zum Einsatz: eine Sekundäranalyse eines multizentrischen RCTs, zwei systematische Übersichtsarbeiten und ein meta-analytischer Strukturgleichungsansatz. Schließlich werden im sechsten und letzten Teil dieser Dissertation die Ergebnisse integriert und zusammenfassend diskutiert. Alles in allem deuten die Befunde dieser Dissertation daraufhin, dass: (a) Digitale Interventionen für die wichtigsten häufigen psychischen Störungen über die Lebensspanne wirksam sind, und einen robusten Trend zu geringeren Effektstärken bei therapeutisch unbegleiteten (im Vergleich zu begleiteten) Interventionen sowie bei jüngeren Altersgruppen (Erwachsene > Jugendliche > Kinder) aufweisen. (b) Nach wie vor erhebliche Unsicherheiten hinsichtlich der Wirksamkeit von Smartphone-basierten Interventionen bestehen. (c) Unterschiedliche Interventionskomponenten zur Wirksamkeit internet-basierter Interventionen beitragen – mit einer herausragenden Bedeutung von menschlicher Unterstützung und Komponenten, welche aktive Bewältigungsstrategien der Patient:innen befördern. (d) Der jeweilige therapeutische Hintergrund und die Störungsspezifität der Intervention sowie das Qualifikationsniveau unterstützender Fachkräfte (sogenannte e-Coaches) keinen Unterschied für die Wirksamkeit digitaler Interventionen bei Angststörungen machen könnten, so wie dies weitere meta-analytische Vergleiche andeuten. (e) Eine Reihe unterschiedlicher Mediatoren die Wirkung der Interventionen vermitteln, und dabei kognitiven Mediatoren bei Depression und Angststörungen offenbar eine herausgehobene Bedeutung zukommt. (f) Über alle Studien und Altersklassen hinweg Selbstwirksamkeit, Akzeptanz, Achtsamkeit, Reduktionen in dysfunktionalen Kognitionen, wahrgenommene Kontrolle sowie Emotionsregulation (insbesondere bei Jugendlichen) als am besten abgesicherte Mediatoren erscheinen. Abschließend werden im Rahmen dieser Dissertation Implikationen für zukünftige Forschung und Empfehlungen für die Methodik kommender Studien abgeleitet und diskutiert, die zu weitreichenderen und robusteren Kausalschlüssen beitragen können.

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„Understanding mechanisms of treatment is the path toward improved treatment."

Alan E. Kazdin (2007)

General introduction

Common mental disorders across the lifespan

The two most prevalent common mental disorders (CMD) worldwide are depression and anxiety (Baxter et al., 2013; Ferrari et al., 2013). Both conditions are among the leading causes of the global burden of disease (Vos et al., 2016), and result in significant personal suffering as well as high socio-economic costs (Mendlowicz & Stein, 2000; Penninx et al., 2021). These findings apply not only for adults, but also hold true for children and adolescents (Reiner et al., 2019). The clinical and public health significance of CMD across the lifespan is further illustrated with the finding that a history of a prior episode of major depression or anxiety early in life is a major risk factor for an additional episode as well as the development of other comorbid mental disorders later in life (Patton et al., 2014).

In specific, major depression has a point prevalence of 4.7% with an annual incidence rate of 3.0% in adults (Ferrari et al., 2013). In high-income countries the lifetime prevalence averages 13.0% (Kessler et al., 2015), with 11.6% in Germany respectively (Busch et al., 2013). The prevalence of depression in children and adolescents is estimated to be 2.6% worldwide (Polanczyk et al., 2015), with increasing incidence rates during adolescence. For example, as close to 14% of adolescents will meet the diagnostic criteria of a depressive disorder before turning to the age of 18 in the US (Merikangas et al., 2010). Moreover, the majority of patients with a recurrent depressive disorder had their first episode during childhood or adolescence (Pine et al., 1998), emphasizing the need for effective early interventions (Cuijpers, Pineda, et al., 2021).

The disease burden of depression in regard to personal distress, quality of life (Strine et al., 2004) as well as economic (Sobocki et al., 2006) and health care costs is substantial (Gilbody et al., 2006). Patients with depression are known to have an elevated risk of early death (Cuijpers & Smit, 2002; Cuijpers et al., 2013; Thapar et al., 2012), due to different factors like high suicide risk (Cuijpers & Schoevers, 2004; Thapar et al., 2012), physical comorbidities (Cuijpers et al., 2014; Härter et al., 2007), as well as increased rates of smoking, substance misuse, and obesity (Thapar et al., 2012). The Global Burden of Disease (GBD) study has revealed that depressive disorders in adults were the third leading cause of disability in 2015 worldwide (Vos et al., 2016) and the second leading cause in 2016 (Vos et al., 2017). Similarly, in young people aged 10-24 years, depressive disorders are among the main contributors to the global burden of disease (Mokdad et al., 2016). Disability-adjusted life

years (DALYs) due to depressive disorders increased from 45.916.000 in 2005 to 54.255.400 in 2015, which represents a change of 18.2% in total (Kassebaum et al., 2016). Future prospects are even more alarming, as unipolar depressive disorders are projected to be the single leading cause of premature mortality and disability in high-income countries with a contribution of almost 10 % of DALYs in total (Mathers & Loncar, 2006). Recent data of the GBD study underpin these findings and trends and highlight the public health significance of depressive disorders overall (Vos et al., 2020).

The group of anxiety disorders (comprising the distinct conditions generalized anxiety disorder, social anxiety disorder/social phobia, panic disorder with or without agoraphobia, specific phobia, separation anxiety disorder and selective mutism according to the DSM-5; American Psychiatric Association, 2013) is the most common class of CMD before depressive disorders (Craske & Stein, 2016). The life-time prevalence rates of anxiety disorders combined in children and adolescents range from 15% to 20% (Zhou et al., 2019), with the onset of the majority of anxiety disorders occurring also within these early developmental periods (Kessler et al., 2005). The cumulative prevalence rates in late adolescence to early adulthood of all anxiety disorders together range from 20% to 30% (15-25 years; Penninx et al., 2021), representing the highest prevalence rates of anxiety disorders across the lifespan. In adulthood, the one-year prevalence is estimated to be 10% to 14% according to DSM criteria, with specific phobia, followed by social anxiety disorder and panic disorder (with or without agoraphobia) being most common (Penninx et al., 2021).

Anxiety disorders have substantial adverse consequences for patients and societies similar to those of depression (Penninx et al., 2021). Anxiety disorders constitute one of the leading causes of disability worldwide (James et al., 2018; Vos et al., 2020; Whiteford et al., 2015) and are associated with enormous personal suffering and impaired quality of life (Mendlowicz & Stein, 2000), high health care and economic costs (Andlin-Sobocki & Wittchen, 2005), high comorbidity with other mental disorders (Bandelow & Michaelis, 2015), as well as an elevated risk for suicidal ideation and behaviors (Sareen et al., 2005). Globally, the group of anxiety disorders accounts for approximately 3.3% of the GBD, and is accountable for approximately €74 billion costs across 30 European countries alone (Gustavsson et al., 2011).

The Covid-19-pandemic had a profound impact on the prevalence rates of both anxiety and depressive disorders, with indications that an additional 53 million cases of major depressive disorder and 76 million cases of anxiety disorders were due to the pandemic in 2020, further aggravating the associated global burden of disease associated with CMD (Santomauro et al.,

2021). At that, children, adolescents and young adults are the age groups that reveal the largest increases in the prevalence rates of depression and anxiety disorders due to the pandemic (Santomauro et al., 2021). Taken together, CMD such as depression and anxiety are not only highly prevalent in different age groups, but are also responsible for enormous personal sufferings and substantial disease burden worldwide (Santomauro et al., 2021; Vos et al., 2020), requiring evidence-based treatments for a timely, accessible and efficient mental healthcare.

Evidence for the effectiveness and uptake of psychotherapies for depression and anxiety in children, adolescents and adults

The evidence base for the efficacy (i.e., do interventions work in highly controlled laboratory settings?) and effectiveness (i.e., do they also work under real-world conditions in routine care?) of several psychotherapies for CMD across age groups is well established and unchallenged. The most comprehensive and extensive empirical support for depression and anxiety disorders, building on hundreds of RCTs, can be found for Cognitive Behavioral Therapy (CBT) (Cuijpers, Quero, et al., 2021; Hofmann et al., 2012). In specific, meta-analytical evidence underscores the effectiveness of CBT for major depression in adults, with medium to large effect sizes ranging from -0.67 compared to treatment as usual (Standardized mean difference, SMD; CI 95%: -0.79 to -0.56) and -0.97 compared to waitlist (SMD; CI 95%: -1.09 to -0.84) (Cuijpers, Quero, et al., 2021). Furthermore, CBT is also effective for depression in children and adolescents (Cuijpers et al., 2020; Zhou et al., 2020). Yet, the effect sizes in these younger age groups are typically smaller, ranging from SMDs -0.22 compared to TAU (children and adolescents combined; CI 95%: -0.67 to 0.23) and -0.94 compared to WL (CI 95%: -1.40 to -0.48; Zhou et al., 2020). The trend of smaller effect sizes in younger age groups can also be observed when comparing the effect sizes specific for adolescents (compared to TAU: Hedges` g = -0.29 (CI 95%: -0.12 to -0.47); compared to WL: g = -0.78 (CI 95%: -0.35 to -1.20)) and for children (compared to TAU: g = -0.13 (CI 95%: 0.07 to -0.33); compared to WL: g = -0.68 (CI 95%: -0.28 to -1.08); Cuijpers et al., 2020). Next to psychotherapies grounded on CBT, psychotherapeutic interventions based on other theoretical orientations are comparably effective in the treatment of major depression in adults. This applies for interpersonal, psychodynamic, life-review, problem-solving, behavioral activation and “third wave” therapies as well as non-directive supportive counseling (Cuijpers, Quero, et al., 2021). In contrast, CBT and interpersonal therapy for

depression in children and adolescents are found to be superior than other psychotherapeutic orientations like problem-solving, psychodynamic or play therapy (Zhou et al., 2015).

The anxiety disorders can be also successfully treated by psychotherapeutic interventions. Meta-analyses indicate that CBT is effective in adults with anxiety disorders, with effect sizes ranging from *g* = -0.80 for GAD (CI 95%: -0.67 to -0.93), *g* = -0.81 for panic disorder (CI 95%: -0.59 to -1.04), and *g* = -0.88 for social anxiety disorder (CI 95%:- 0.74 to -1.03) when compared to combined control conditions (i.e., TAU, WL and Pill placebo) (Cuijpers et al., 2016). Similarly to depression, the effect sizes for CBT in the treatment of anxiety are usually smaller in children and adolescents (SMD -0.40; CI 95%: -1.01 to 0.20 compared against TAU; Zhou et al., 2019). Furthermore, group CBT was evaluated to be more effective than individual CBT (SMD -0.44; CI 95%: -0.82 to -0.06) in a network-meta-analysis on anxiety disorders in youth (Zhou et al., 2019). Other psychotherapeutic orientations, such as psychodynamic therapy, are also effective in the treatment of anxiety in adults, for example in the case of social anxiety disorder (Mayo-Wilson et al., 2014); yet, psychodynamic approaches evince smaller effect sizes than CBT (SMD for CBT: -1.19 CI 95%: -1.56 to -0.81; vs. SMD for psychodynamic therapy: -0.62 CI 95%: -0.93 to -0.31) when compared to waitlist and are also evaluated to be less effective in the direct comparison with CBT (SMD for CBT: -0.56 CI 95%: -1.03 to -0.11) in a network-meta-analysis specific for social anxiety disorder (Mayo-Wilson et al., 2014). Next to the interventions` effectiveness, CBT is also found to be acceptable (i.e., defined as all-cause dropout rate) (Cuijpers, Quero, et al., 2021; Zhou et al., 2020; Zhou et al., 2019), and sustains treatment effects at 12-months-follow-up for depression (Cuijpers, Quero, et al., 2021) and for several anxiety disorders (i.e., for generalized anxiety disorder, social anxiety disorder and PTSD; but not for panic disorder with or without agoraphobia) (van Dis et al., 2020). In sum, national treatment guidelines recommend evidence-based psychotherapies like CBT as first line treatments for depression (AWMF, 2022; NICE, 2022) and anxiety disorders (AWMF, 2021; NICE, 2019) in Germany and the UK .

However, the biggest drawback and unsolved problem in mental health care is that only a minority of patients are able to access and receive any form of evidence-based psychotherapy (Andrade et al., 2014). This substantial treatment gap can be found in low-, middle- as well as in high-income countries around the world and is largely due to a range of structural and individual barriers to treatment (Andrade et al., 2014). Structural barriers comprise for example the shortage of mental health care services, long waiting times and high treatment costs for face-to-face psychotherapies (Andrade et al., 2014; Gulliver et al., 2010; Mohr et al.,

2010). Individual barriers to treatment comprise for instance limitations in mobility and time, prejudices about therapists and treatments, or fear of stigmatization (Andrade et al., 2014; Gulliver et al., 2010; Mohr et al., 2010).

Given the limited uptake of evidence-based psychotherapies for CMD across the lifespan, novel interventions and innovative delivery formats of mental healthcare services – that are effective, acceptable and scalable for large number of patients – may contribute to overcome these barriers to evidence-based treatment in different age groups globally. Considering the ubiquitous proliferation of the Internet and smartphones worldwide, technological approaches and innovative ways to deliver mental health interventions were explored in the past two decades, with pioneering countries like Australia or Sweden paving the way for a global upsurge in digital mental health research (Andersson et al., 2019; Titov et al., 2020).

Digital mental health

Digital mental health interventions (alternatively referred to as DMHI, digital interventions or Internet- and mobile-based interventions (IMIs) in the following chapters of this dissertation) are defined as psychological, psychotherapeutic or behavioral health interventions that are implemented by technological means and are based on evidence-based health-related content with the overarching aim to improve mental health. These rather novel interventions can be differentiated by their technical implementation (e.g., smartphone-, tablet- or computer-based), way of application (e.g., stand-alone or blended care), degree of human support (e.g., pure self-help intervention, technical or therapeutic support, or psychotherapy via video calls) and theoretical foundation (e.g., CBT, mindfulness-based, acceptance and commitment therapy or psychodynamic approaches; Domhardt et al., 2018, 2019; Domhardt, Messner, et al., 2021; Ebert et al., 2018). The majority of scientifically investigated digital interventions are internet-based self-help interventions that are implemented either without any support (unguided) or with some type and amount of support (guided interventions). Yet and more recently, smartphone- or mobile-based interventions (i.e., mental health apps) are increasingly researched for mental disorders (Torous et al., 2021). Most of these digital interventions are built on CBT principles and are delivered with several thematic coherent intervention components or modules (Barak et al., 2009; Domhardt et al., 2018, 2019; Domhardt, Messner, et al., 2021). Common to most digital interventions is their aim to alter cognitive, behavioral and affective processes in the individual person, to create positive behavior and symptom change, improve knowledge, awareness and understanding by means of the delivery of health-

related material. Furthermore, the intention to support the transfer of these adaptations and acquired skills into the daily lives of users is supported with the use of (inter)active components and deployment of internet- and mobile-based just-in-time techniques in some latest digital interventions (Torous et al., 2021).

By exploiting these specific features, digital interventions are thought to overcome the aforementioned barriers to treatment, and contribute to the advancement and extension of evidence-based mental healthcare services worldwide. Hereby, several advantages and assets of digital interventions compared to conventional psychotherapies delivered face-to-face might be key for reducing the profound treatment gap in mental health across the lifespan: 1) delivery independent from space and time, 2) possible anonymity, 3) low-threshold access, 4) convenience of treatment (e.g., advancement in own pace or possible repetitions), 5) flexibility of treatment, 6) integration into daily life with the possibility of adaptive just-in-time interventions, 7) self-efficacy and empowerment emphasis, 8) both high treatment fidelity by standardization and treatment individualization (i.e., tailoring) as well as 9) potential cost-effectiveness and (10) scalability (Domhardt et al., 2018, 2019, 2023; Domhardt, Messner, et al., 2021; Ebert et al., 2018).

The efficacy and effectiveness of digital interventions for depression across age groups was evaluated by a meta-analytical review of 83 studies comprising 15,530 individual patients (Moshe et al., 2021). A major strength of this meta-analysis was the focus on studies that investigated participants with clinically relevant symptoms of depression only, in contrast to other reviews on studies relying on community or convenience samples comprising participants with subthreshold depression, mixed disorders or without any pathology. In the most comprehensive meta-analysis on digital interventions for depression conducted to date, digital interventions with various theoretical foundations (but a majority with a CBT-orientation) were evaluated to be efficacious with a medium overall effect size when compared to various active and passive control conditions combined (g = 0.52; 95% CI: 0.43 to 0.60), with treatment effects also sustained at follow-up (Moshe et al., 2021). Subgroup analyses revealed significant differences between interventions and different control conditions (WL: g = 0.70; 95% CI: 0.58 to 0.60; attention control: g = 0.83; TAU: g = .31; 95% CI: 0.21 to 0.41), significantly higher effect sizes in interventions that involved human therapeutic guidance (g = 0.63; 95% CI: 0.50 to 0.76) compared with self-help interventions (g = 0.34; 95% CI: 0.24 to 0.45) and interventions with technical guidance (g = 0.46; 95% CI: 0.29 to 0.62), and significantly lower effect sizes for effectiveness trials (g = 0.30; 95% CI: 0.15 to 0.35) compared with efficacy trials (g = 0.59; 95% CI: 0.50 to 0.69). No significant

difference in outcomes due to the technical implementation (i.e., between mobile-based, computer- and internet-based interventions) and no significant difference between human-guided digital interventions and face-to-face psychotherapy for depression were found, although the number of studies in these two comparisons was low (Moshe et al., 2021). Since only three studies evaluated a direct comparison between digital interventions and face-to-face-psychotherapy it seems too soon to conclude that digital interventions are as equally effective as face-to-face psychotherapy for the treatment of depression (Moshe et al., 2021). Similarly to the evidence base of face-to-face psychotherapies (Cuijpers et al., 2020), this meta-analysis revealed a significantly lower effect size for children and adolescents than for adults (g = 0.15 vs. g = 0.53), although only four studies recruited children and adolescents with depression, precluding definite conclusions on the efficacy of digital interventions for these younger age groups (Moshe et al., 2021). Further knowledge gaps were identified for the efficacy and effectiveness on comorbid depressive symptoms in specific patient populations, for example in youth with chronic medical conditions as well as for adults with chronic back pain. This information is relevant, in order to grasp the potential of digital interventions in highly burdened populations and contribute to the personalization of psychotherapeutic interventions and precision digital mental health (Moshe et al., 2021).

The efficacy and effectiveness of internet-based CBT (iCBT) interventions for the group of anxiety disorders was evaluated by a Cochrane review (Olthuis et al., 2016). In this systematic review and meta-analysis of 38 studies with 3214 participants, iCBT was evaluated to be effective at post-treatment both for disorder-specific symptoms (SMD = -1.06; 95% CI: -1.29 to -0.82) and general anxiety symptoms (SMD = -0.75; 95% CI: -0.98 to -0.52). Furthermore, a meta-analysis specific for distinct anxiety disorders revealed SMDs of g = 0.70 for GAD (95% CI: 0.39 to 1.0), g = 1.31 for panic disorder (95% CI: 0.85 to 1.8), and g = 0.92 (95% CI: 0.75 to 1.1) for social anxiety disorder, with effect sizes representing medium to large effects in favor of computerized and internet-based CBT (Andrews et al., 2018). Another meta-analytic review was dedicated to evaluate the efficacy of mobile-based interventions for anxiety symptoms in adults (Firth et al., 2017). In this meta-analysis of nine studies, significantly greater reductions in anxiety symptom severity were observed for mobile-based interventions than control conditions (g = 0.33; 95% CI: 0.17 to 0.48). Effect sizes for mobile-based interventions were significantly higher when compared to inactive control conditions (g = 0.45; 95% CI: 0.30 to 0.61) than active control conditions (g = 0.19; 95% CI: 0.07 to 0.31). Finally, there are first meta-analytic indications (Rooksby et al., 2015) that digital

interventions and iCBT can be also efficacious for anxiety symptoms in children and adolescents when compared to wait-list control (SMD = 0.69; 95% CI: 0.44 to 0.94.).

At the time during the conduction of this dissertation, no meta-analysis has evaluated the effectiveness of digital interventions for patients with an established diagnosis of panic disorder with or without agoraphobia. However, this knowledge is important to assess the "real-world" potential of digital interventions under routine healthcare conditions (i.e., effectiveness) for patient groups with clinically relevant symptomatology (in contrast to often highly selected participant samples in efficacy studies). Further knowledge gaps were about the efficacy of mobile-based interventions for youth with CMD as well as integrative and comprehensive knowledge of the effect sizes for various CMD in children and adolescents. However, probably one of the most important unsolved research question for the evidence base of digital interventions for CMD across the lifespan is the lack of comprehensive and integrated empirical knowledge on the active ingredients and mechanisms of change of these interventions. Yet, knowledge *whereby* and *how* psychotherapeutic interventions work is a central constituent of evidence-based medicine and of empirically-supported treatments in general (Borkovec et al., 1998; Cuijpers, Reijnders, & Huibers, 2019; Kazdin, 2007).

Mechanisms of change and psychotherapy process research

Evidence-based insights on the active ingredients and therapeutic processes of interventions is of high scientific and clinical relevance, because this knowledge can be utilized for several matters, as highlighted by Alan Kazdin in his seminal paper in 2007. 1) The probably most important implication of this knowledge is that it is key for the empirically-supported advancement of interventions and improvement of treatment outcomes. Knowledge *whereby* (i.e, the intervention components that induce therapeutic change representing the active ingredients of interventions) and *how* (i.e., the mechanisms and processes of change within patients that are statistically ascertained by mediators) psychological and psychotherapeutic interventions work can inform the development of augmented interventions, relying on essential active components, which induce crucial change mechanisms in patients, resulting in better treatment outcomes eventually (Kazdin, 2007). 2) Understanding the working mechanisms of specific interventions can also bring parsimony among the plentitude of psychological interventions with different theoretical foundations that have either an empirical underpinning or not (Kazdin, 2007). 3) Disentangling the mechanisms of change (more recently labelled rather as processes of change; Hofmann & Hayes, 2019) will elucidate

the relations between what actually occurs during treatment and the association of treatment types with a variety of outcomes (Kazdin, 2007). 4) The dissemination of psychotherapeutic interventions from research into routine mental healthcare practices would be difficult without understanding how treatment works. To optimize the generalization of treatment effects from research to clinical practice, the knowledge is crucial what makes treatment work, and what components must not be lessened to achieve change – while removing unnecessary or redundant components (Kazdin, 2007). 5) Insights how therapy works can also contribute to identify moderators of treatment and thereby contribute to the personalization of psychotherapy and digital mental health (Kazdin, 2007). 6) Understanding the therapeutic processes through which treatment operates can also help sort through those aspects that might be particularly influential on treatment outcome and allow for improved pre-treatment selection of patients, securing that each patient receives the type (and modality) of intervention that has the highest chances of success (Kazdin, 2007). 7) Finally, processes that elaborate how psychological and psychotherapeutic interventions work might have generality for understanding human functioning beyond the setting of treatment, and might also inform etiological theories of disorders (Kazdin, 2007).

Empirical knowledge on the mechanisms of change in psychotherapies and digital interventions can be attained primarily by two research methods: component studies and mediation studies (Domhardt, Steubl, et al., 2021). The so called component studies aim to determine the influence of single intervention components on treatment effects, thereby contributing to the understanding *whereby* psychotherapeutic interventions work (Cuijpers, Reijnders, & Huibers, 2019; Domhardt, Steubl, et al., 2021). In component studies, psychotherapeutic interventions with multiple modules or components are compared with untangled variations of the same intervention (Borkovec et al., 1998) in which either a component is left out (i.e., dismantling studies) or added to the full treatment package (i.e., additive design studies; Domhardt, Steubl, et al. 2021). In case a dismantling study is conducted as a randomized controlled trial (RCT) and fulfills the respective quality criteria associated with RCTs, the study can generate strong causal evidence on the distinct effects of single intervention components (Cuijpers, Cristea, et al., 2019; Domhardt, Steubl, et al., 2021). Significant intervention components that contribute to the efficacy of treatment can be considered as “active ingredients” of therapies. They can be further differentiated into so called specific or common factors of psychotherapies (Domhardt, Steubl, et al., 2021; Mulder et al., 2017). Specific factors are those therapeutic methods and standard techniques that are characteristic for a certain therapeutic approach, based on the respective model of

psychotherapy and/or delineated from a disorder-specific etiological model (DeRubeis et al., 2005; Domhardt, Steubl, et al., 2021). Prominent examples for specific factors are cognitive restructuring and behavioral activation related to CBT, or defensive and reflective functioning related to psychodynamic therapies (Domhardt, Steubl, et al., 2021). On the contrary, common factors are thought to be generally present in psychotherapeutic interventions, irrespective of the specific therapeutic approach and theoretical orientation (Domhardt, Steubl, et al., 2021; Wampold, 2015). Paradigmatic examples of common factors are the therapeutic alliance between patients and therapists, or patient expectations and hope. The debate about the relative importance of specific and common factors in psychotherapy process research appears to head to the common ground that both, specific and common factors, – as well as their respective interactions – contribute to successful therapies and treatment efficacy (Domhardt, Steubl, et al., 2021; Mulder et al., 2017; Tschacher et al., 2014).

Nonetheless, the findings of component studies do not necessarily reveal *how* psychotherapies operate, and which therapeutic processes within patients lead to change (Domhardt, Steubl, et al., 2021). Mediation studies (or mediation analyses) contribute to these questions (Kazdin, 2007, 2009) and can be viewed as the crucial approach of psychotherapy process research and the essential method to study mechanisms of change in psychological interventions (Domhardt, Steubl, et al., 2021). Mediators are intervening variables that account statistically for the relationship between a psychotherapeutic intervention and an outcome (Kazdin, 2007), and thereby potentially hint at mechanisms through which the intervention achieves its effects (Domhardt, Steubl, et al., 2021; Kraemer et al., 2002). Well-established examples of mediators in psychotherapy for CMD are the concepts of perceived control, functional cognitions or the application of skills (Domhardt, Steubl, et al., 2021). However, it is imperative to keep in mind that mediators might be congruent and identical to a specific mechanism of change (i.e., the definite process accountable for treatment change), but might also be a proxy for one or more other variables that do not explain the assumed mechanism (Domhardt, Steubl, et al., 2021; Kazdin, 2007). These proxy variables are either unknown and/or unmeasured, or both known and measured, with subsequent implications for the scope of causal inferences (Ohlsson & Kendler, 2019). Thus, in the context of mediation studies, it is valuable that mediators are deduced theoretically (i.e., conceptually represent a plausible change mechanism that is induced by an intervention component), are defined and operationalized a priori, are statistically tested against other known potential intervening variables and reveal a strong statistical association (between intervention, mediator and outcome) (Domhardt, Steubl, et al., 2021; Johansson & Høglend, 2007; Kazdin, 2007;

Kraemer et al., 2002; Laurenceau et al., 2007). Further important quality criteria for psychotherapy process research according to Kazdin (2007, 2009) are: The criteria of specificity (of the association between intervention, mediator and outcome), gradient (i.e., dose-response relationship between mediator and outcome) and consistency (of results on mediators across studies). Additionally, findings of mediation studies are enormously strengthened when they result from an experimental design (Domhardt, Steubl, et al., 2021). This can be achieved either by randomly assigning adequate numbers of participants to different comparison conditions in an RCT (Laurenceau et al., 2007), or by directly manipulating the mediator variable itself (Kazdin, 2007). In the latter approach, it is safe to assume that the experimental variation of the mediator causally leads to the observed changes in the outcome, whereas in the former approach one can merely presume that the intervention effects are mediated by the purported construct and not by other conceptually differing proxy variables (Domhardt, Steubl, et al., 2021). The most important criterion and basic prerequisite to assume causality, however, is temporal precedence (Domhardt, Steubl, et al., 2021). The essential criterion of temporal precedence is met, when a timeline can be established that the intervention leads to changes in the mediator, and the changes in the mediator precede changes in the outcome – and not vice versa (Domhardt, Steubl, et al., 2021; Kazdin, 2007; Kraemer et al., 2008). Hence, only longitudinal study designs with several concurrent assessments of the mediator and outcome variables with at least three measurement points are assumed to be suitable to evaluate this criterion and establish the actual directionality and shape of change (Domhardt, Steubl, et al., 2021; Laurenceau et al., 2007). Altogether, multiple converging lines of process research adhering to these criteria and resorting to different methodologies (e.g., both component and mediation studies), while addressing the same or closely related questions (i.e., triangulation; Munafò & Davey Smith, 2018), are necessary to identify specific mechanisms of change and to approach causality (Domhardt, Steubl, et al., 2021; Kazdin, 2007, 2009; Ohlsson & Kendler, 2019).

Yet, this knowledge is largely pending in digital mental health. Given the importance of the knowledge on the active ingredients and mechanisms of change outlined above, it is high time to extend and synthesize empirically based insights on the therapeutic processes of digital interventions for CMD across age groups.

Objectives and outline of this thesis

The overarching aim of this dissertation is to contribute to the identification of the active ingredients and mechanisms of change in digital interventions for CMD across the lifespan. In detail, the specific objectives of this dissertation are,

1. to systematically review and meta-analytically evaluate the empirical evidence on the efficacy and effectiveness of digital interventions for certain CMD across the lifespan that have a limited evidence base so far, as a fundamental prerequisite and starting point for all subsequent research on change mechanisms;
2. to develop and designate an integrative conceptual model of the mechanisms of change in digital interventions for depression, as a principal and coherent framework for research on change mechanisms;
3. to identify and discuss the possibilities and challenges of digitalized approaches to psychotherapy process research;
4. to synthesize and meta-analytically evaluate the components of digital interventions for anxiety disorders, in order to identify the active ingredients of interventions;
5. to explore, review and evaluate the mediators and mechanisms of change in digital interventions for the prevention and treatment of CMD (with a particular focus on depression and anxiety) across the lifespan.

Accordingly, knowledge derived from this thesis might contribute to the evidence-based advancement of digital interventions, eventually leading to augmented interventions with higher effectiveness and improved treatment outcomes for different patient groups and populations (Figure 1).

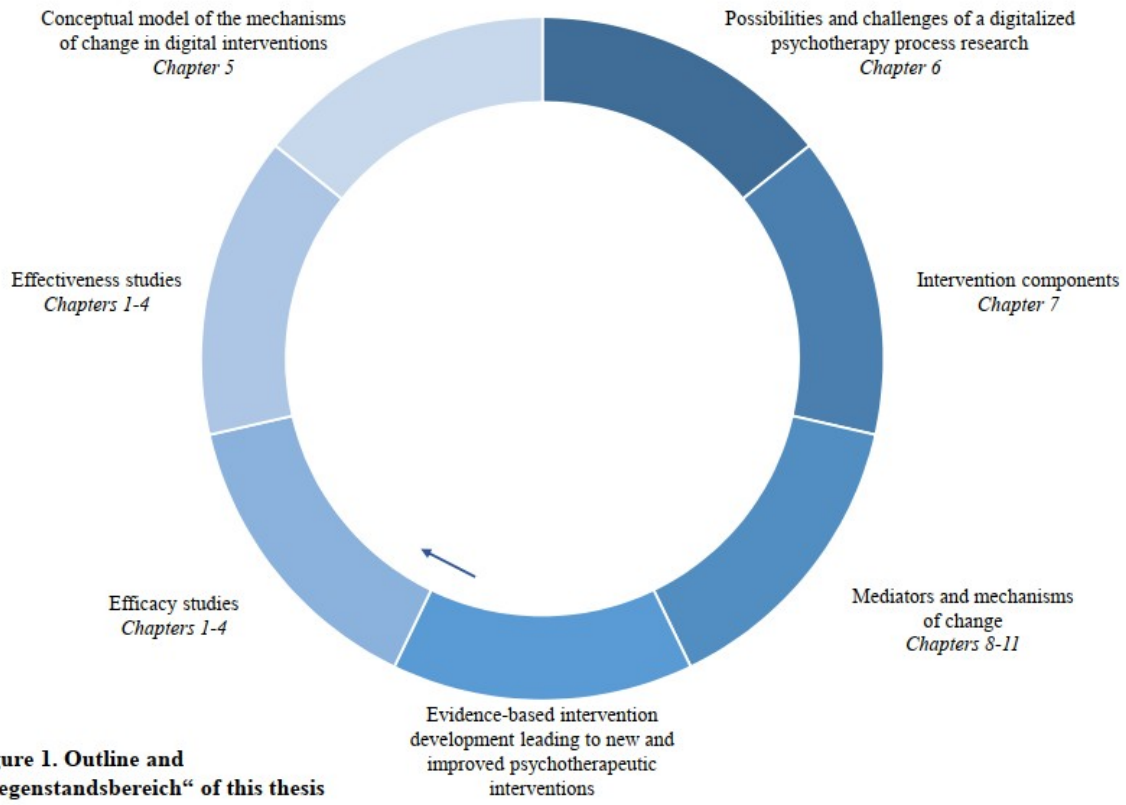


Figure 1. Outline and „Gegenstandsbereich“ of this thesis

In order to address each research question adequately and to maximize the knowledge to be gained, several methodological approaches and types of studies were deployed in this thesis – with a particular focus on systematic reviews and meta-analyses of RCTs, enabling the best-available, integrative and highest level of evidence on the efficacy and effectiveness of psychological interventions (Leichsenring et al., 2019). RCTs are the most important study type for evidence-based medicine and mental health. In these studies, participants are randomly assigned either to the intervention condition or one (or more) control condition(s), are masked to the condition they are assigned to, in order to evaluate the efficacy (under highly controlled laboratory conditions) or effectiveness (under real-world conditions) of an intervention (Schulz et al., 2010). Systematic reviews synthesize the research findings of single RCTs with standardized methods, which are thought to help to minimize bias, deliver reliable and precise findings and lead to justified conclusions (Higgins et al., 2019). Ideally, systematic reviews deploy a priori defined objectives, pre-registered inclusion and exclusion criteria for the primary studies of interest, reproducible systematic searches of studies and applied methodologies, an evaluation of the quality of primary studies, as well as a systematic (narrative or statistical) synthesis and presentation of the findings (Higgins et al., 2019).

Meta-analyses do statistically evaluate and synthesize the results of single studies within the framework of a systematic review (Higgins et al., 2019).

The first part of this dissertation presents the results of four systematic review studies, designed to evaluate the efficacy and effectiveness of digital interventions for a variety of mental disorders, especially for those with limited empirical knowledge so far. This is important, because the establishment that a psychological intervention is effective (or not), is a fundamental prerequisite for all succeeding process research on change mechanisms. In specific, **Chapter 1** integrates the available meta-analytic evidence on the efficacy and effectiveness of digital interventions for CMD in children and adolescents. **Chapter 2** presents the results of a meta-analysis on the effectiveness of digital interventions for adults suffering from diagnosed panic disorder with or without agoraphobia, and **Chapter 3** the meta-analytical findings of the efficacy of digital interventions for youth with chronic medical conditions and comorbid symptoms of CMD. **Chapter 4** describes the results of a systematic evaluation of mental health apps for depression, anxiety and PTSD in children and adolescents with two standardized rating scales. **Chapter 5**, representing the second part of this dissertation, describes the development of an integrative conceptual model of the mechanisms of change in digital interventions for depression in a narrative review. The third part of this dissertation was published as **Chapter 6** and outlines the possibilities and challenges of digitalized means in psychotherapy process research in a perspective article. **Chapter 7** describes the results of a meta-analytic review of the intervention components of IMIs for anxiety, and identifies potential specific and common factors as active ingredients of digital interventions. Part V represents the core and central part of this thesis and comprises four chapters, all dedicated to investigate the mediators and mechanisms of change in digital interventions. In specific, **Chapter 8** explores the mechanisms of change in a digital intervention to prevent depression-onset in patients with chronic back pain and describes the findings derived from a multicenter RCT. **Chapter 9** outlines the results of a systematic review on the mechanisms of change in digital interventions for CMD in youth. **Chapter 10** highlights the findings of the first meta-analytic structural equation modeling approach on the mediators and therapeutic processes in digital interventions for anxiety. **Chapter 11** is the first systematic review on the mediators and mechanisms of change in various Internet- and mobile-based interventions for depression. Finally, the sixth and last part of this dissertation discusses and integrates the findings of the publications on which this thesis is built on.

Part I

Efficacy and effectiveness of digital interventions for common mental disorders across the lifespan

Part I comprises the following chapters, published as:

Chapter 1. Domhardt, M., Steubl, L., & Baumeister, H. (2020). Internet- and mobile-based interventions for mental and somatic conditions in children and adolescents: A systematic review of meta-analyses. *Zeitschrift für Kinder- und Jugendpsychiatrie und Psychotherapie, 48*, 33-46. https://doi.org/10.1024/1422-4917/a000625

Chapter 2. * Domhardt, M., Letsch, J., Kybelka, J., Koenigbauer, J., Doebler, P., & Baumeister, H. (2020). Are Internet- and mobile-based interventions effective in adults with diagnosed panic disorder and/or agoraphobia? A systematic review and meta-analysis. *Journal of Affective Disorders, 276*, 169-182. https://doi.org/10.1016/j.jad.2020.06.059

Chapter 3. * Domhardt, M., Schröder, A., Geirhos, A., Steubl, L., & Baumeister, H. (2021). Efficacy of digital health interventions in youth with chronic medical conditions: A meta-analysis. *Internet Interventions, 24*, 100373. https://doi.org/10.1016/j.invent.2021.100373

Chapter 4. Domhardt, M., Messner, E.-M., Eder, A.-S., Engler, S., Sander, L. B., Baumeister, H., & Terhorst, Y. (2021). Mobile-based interventions for common mental disorders in youth: A systematic evaluation of pediatric health apps. *Child and Adolescent Psychiatry and Mental Health, 15*(1), 49. https://doi.org/10.1186/s13034-021-00401-6

Central chapters are marked with an asterisk.

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Chapter 1

Internet- and mobile-based interventions for mental and somatic conditions in children and adolescents: A systematic review of meta-analyses

This chapter is published as:

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Review

Internet- and Mobile-Based Interventions for Mental and Somatic Conditions in Children and Adolescents

A Systematic Review of Meta-analyses

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Abstract: This meta-review integrates the current meta-analysis literature on the efficacy of internet- and mobile-based interventions (IMIs) for mental disorders and somatic diseases in children and adolescents. Further, it summarizes the moderators of treatment effects in this age group. Using a systematic literature search of PsycINFO and MEDLINE/PubMed, we identified eight meta-analyses (N = 8,417) that met all inclusion criteria. Current meta-analytical evidence of IMIs exists for depression (range of standardized mean differences, SMDs = .16 to .76; 95% CI: –.12 to 1.12; k = 3 meta-analyses), anxiety (SMDs = .30 to 1.4; 95% CI: –.53 to 2.44; k = 5) and chronic pain (SMD = .41; 95% CI: .07 to .74; k = 1) with predominantly nonactive control conditions (waiting-list; placebo). The effect size for IMIs across mental disorders reported in one meta-analysis is SMD = 1.27 (95% CI: .96 to 1.59; k = 1), the effect size of IMIs for different somatic conditions is SMD = .49 (95% CI: .33 to .64; k = 1). Moderators of treatment effects are age (k = 3), symptom severity (k = 1), and source of outcome assessment (k = 1). Quality ratings with the AMSTAR-2-checklist indicate acceptable methodological rigor of meta-analyses included. Taken together, this meta-review suggests that IMIs are efficacious in some health conditions in youths, with evidence existing primarily for depression and anxiety so far. The findings point to the potential of IMIs to augment evidence based mental healthcare for children and adolescents.

Keywords: eHealth, mHealth, psychotherapy, youth, meta-review

Internet- und mobilebasierte Interventionen psychischer Störungen und körperlicher Erkrankungen im Kindes- und Jugendalter: eine systematische Übersicht der meta-analytischen Evidenz

Zusammenfassung: Die vorliegende Übersichtsarbeit fasst die aktuelle meta-analytische Evidenz zur Wirksamkeit internet- und mobilebasierter Interventionen (IMIs) für psychische Störungen und körperliche Erkrankungen im Kindes- und Jugendalter zusammen. Darüber hinaus soll der derzeitige Wissensstand über mögliche Moderatoren dieser vergleichsweise neuen Interventionsform zusammengetragen werden. Mittels einer systematischen Literaturrecherche in den Datenbanken PsycINFO und MEDLINE/PubMed konnten acht Meta-Analysen (N = 8.417) identifiziert werden, die sämtliche Einschlusskriterien erfüllen. Effektstärken von IMIs im Vergleich zu vorwiegend inaktiven Kontrollgruppen (Warteliste; Placebo) liegen vor für die Bereiche Depression (Bandbreite standardisierter Mittelwertsdifferenzen, SMD = .16 bis .76; 95%–KI: –.12 bis 1.12; k = 3 Meta-Analysen), Angststörungen (SMD = .30 bis 1.4; 95%–KI: –.53 bis 2.44; k = 5) und chronischem Schmerz (SMD = .41; 95%–KI: .07 bis .74; k = 1). Die Effektstärke für IMIs über verschiedene psychische Störungen hinweg beträgt SMD = 1.27 (95%–KI: .96 bis 1.59; k = 1); die Effektstärke für IMIs bei verschiedenen somatischen Erkrankungen liegt bei SMD = .49 (95%–KI: .33 bis .64; k = 1). Als signifikante Moderatoren konnten das Alter (k = 3), der Symptomschweregrad (k = 1) und die Art der Ergebnisevaluation (k = 1) identifiziert werden. Die Bewertung der methodischen Qualität der eingeschlossenen Meta-Analysen anhand der AMSTAR-2-Checkliste ergab insgesamt eine akzeptable methodische Güte. Zusammenfassend deutet diese Übersichtsarbeit auf die Wirksamkeit von IMIs bei verschiedenen Erkrankungen hin, wobei bislang aktuell überwiegend Evidenz zu depressiven Störungen und Angststörungen existiert. Dabei weisen die Ergebnisse auf das Potenzial dieser neuen Behandlungsform für eine mögliche Erweiterung der evidenzbasierten Gesundheitsversorgung für Kinder und Jugendliche mit psychischen Störungen hin.

Schlüsselwörter: eHealth, mHealth, Psychotherapie, Adoleszenz, Review

Introduction

The internet and its applications on mobile devices are today omnipresent in many peoples' daily life. This is especially true for many children and adolescents, who from their very beginning are familiar with an increasingly digitalized world. The fluency with, and the attractiveness of, the internet and its digital opportunities might prove to be such a key asset as to resort to these new media also in pediatric healthcare. Innovative treatment options and the ex-

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tensions of existing practices for common mental disorders and somatic diseases are urgently needed, as uptake rates and service utilization of conventional evidence based psychological treatments are low in children and adolescents (Chavira, Stein, Bailey, & Stein, 2004; Costello, He, Sampson, Kessler, & Merikangas, 2014; Essau, 2005; Merikangas et al., 2011; Zachrisson, Rödje, & Mykletun, 2006). Structural barriers to the uptake of face-to-face treatments lie, for example, in the shortage of healthcare services, long waiting times, and high treatment costs (Andrade et al., 2014; Gulliver, Griffiths, & Christensen, 2010; Mohr et al., 2010); individual barriers comprise limitations in mobility and time, prejudices about therapists and treatments, and fear of stigmatization (Andrade et al., 2014; Gulliver et al., 2010; Mohr et al., 2010).

Internet- and mobile-based interventions (IMIs) offer several advantages over conventional approaches and might contribute to overcoming these treatment barriers, leading to a more comprehensive evidence based healthcare for children and adolescents (Andersson & Titov, 2014; Emmelkamp et al., 2014). This review defines IMIs as predominantly self-guided psychosocial interventions implemented by means of a prescriptive online program or mobile-based app, used by individuals seeking health-related support (Barak, Klein, & Proudfoot, 2009; Domhardt, Ebert, & Baumeister, 2018). These interventions aim to create positive behavior and symptom change, improve knowledge, awareness, and understanding by means of the delivery of health-related material, use of (inter)active components, and deployment of internet- and mobile-based therapeutic techniques (Barak et al., 2009; Domhardt et al., 2018). IMIs can be implemented as stand-alone interventions (Ebert et al., 2018), as part of a blended-therapy approach (Erbe, Eichert, Riper, & Ebert, 2017), or as low-intensity intervention in a stepped-care model (Domhardt & Baumeister, 2018), partly also called a sequential stepping-up blended therapy approach (Ebert et al., 2018; Erbe et al., 2017).

A major advantage of IMIs compared to conventional psychosocial interventions is their ability to be integrated flexibly into the daily life of the user, irrespective of the constraints of space and time. They may decrease time for travel and administration, reduce stigma threat by preserving anonymity, and allow individuals to work at their own pace with automated feedback on personal progress consecutively. Furthermore, IMIs might be particularly attractive from a public-health perspective, given their presumed potential with regard to scalability and cost-effectiveness (Andersson & Titov, 2014; Emmelkamp et al., 2014).

The evidence base of IMIs for most common-mental and some somatic disorders in adulthood has been firmly established. Solid and further growing evidence indicates that IMIs are efficacious in the treatment of depression (e.g., Königbauer, Letsch, Doebler, Ebert, & Baumeister, 2017; Richards & Richardson, 2012) and anxiety disorders (e.g., Arnberg, Linton, Hultcrantz, Heintz, & Jonsson, 2014; Olthuis, Watt, Bailey, Hayden, & Stewart, 2016), with comparable effect sizes to conventional face-to-face therapies at posttreatment (Andersson, Cuijpers, Carlbring, Riper, & Hedman, 2014). Further meta-analytic evidence for the efficacy of IMIs was found for a range of other mental disorders such as posttraumatic stress disorder (Kuester, Niemeyer, & Knaevelsrud, 2016), obsessive-compulsive disorder (Dèttore, Pozza, & Andersson, 2015), and eating disorders (Melioli et al., 2016). There is also evidence from randomized controlled trials that IMIs work in the (co)treatment for some somatic conditions with significant psychosocial aspects (Andersson, 2016; Bendig et al., 2018). Among these somatic diseases are chronic pain (Baumeister et al., 2015; Lin et al., 2017), diabetes (Ebert et al., 2017; Nobis et al., 2015), and tinnitus (Andersson, 2015; Andersson, Strömgren, Ström, & Lyttkens, 2002) – to name only a few.

Compared to the empirical foundation of IMIs in numerous conditions for adults, the evidence base of IMIs for mental disorders and somatic diseases in children and adolescents is rather narrow, but evolving, given a range of recent randomized controlled trials (e.g., Spence, Donovan, March, Kenardy, & Hearn, 2017; Stjerneklar, Hougaard, Nielsen, Gaardsvig, & Thastum, 2018; Yap et al., 2018) and the particular dynamics in this research domain. Still, comprehensive and integrated meta-analytic knowledge on the efficacy of IMIs for children and adolescents in various health conditions is pending, as the only review of meta-analyses (i.e., meta-review) published so far is confined to mental disorders (Hollis et al., 2017) and characterized by the simultaneous consideration of diverse on- and offline-based technology-delivered interventions. Moreover, important research questions about the specific factors, design features, and developmentally necessary adaptations of IMIs for this young target group are largely unsettled to date, and the generalizability of findings from adult populations is questionable. Most prominently, information about the required intensity and amount of human support ("guidance") provided by e-coaches and caregivers in these online-based self-help interventions for children is essential (Baumeister, Reichler, Munzinger, & Lin, 2014). Scientifically informed knowledge about this and other issues is central to maximizing treatment outcomes and warranting the safety of internet-based interventions for children and adolescents.

In this systematic review, we aim 1) to provide a comprehensive overview of meta-analyses on the efficacy of IMIs for common mental disorders and somatic diseases in children and adolescents. By critically evaluating the existing meta-analyses in this field, we also intend 2) to identify specific (design) features, intervention components

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and factors that are associated with the efficacy of IMIs in this younger age group (i.e., moderators of treatment effects) as well as 3) to highlight key areas for future research. The meta-review approach was chosen in order to provide readers with a comprehensive overview on the broad scope of IMIs for mental disorders and somatic diseases in children and adolescents.

Methods

Inclusion Criteria

Meta-analyses were eligible for inclusion if they met all of the following criteria:

Population: (1) Meta-analyses focused on studies with children and adolescents (aged 0–18 years). (2) Participants met diagnostic criteria according to a classification system (e.g., ICD-10, DSM-IV, or DSM-5) for at least one mental disorder or somatic disease, or indicated significant symptom burden assessed by means of self- or observer- report data.

Intervention: (3) Meta-analyses investigated psychosocial interventions that are internet or mobile based (e.g., through webpages, e-mail, chat, videoconference, mobile app, or instant messaging). These IMIs could have been complemented with an initial face-to-face contact or regular phone calls if the main part (i.e., more than half of the time invested per participant) of the intervention was carried out online. Computerized or technology-delivered psychosocial interventions eligible for inclusion had at least one intervention component provided via the internet. (4) Furthermore, IMIs had a psychotherapeutic orientation and were based on an established psychotherapeutic approach, as defined by Kampling and colleagues (2014). Health behavior modification approaches had to be in a direct relation to a present somatic condition. Meta-analyses on IMIs with a prevention or rehabilitation focus were not included, because we wanted to specifically concentrate on psychosocial interventions delivered in an online setting addressing clinically relevant symptoms of common mental disorders or somatic diseases.

Control group: (5) Meta-analyses had to include studies with an active (e.g., face-to-face intervention, other IMI) or passive control group (e.g., placebo, treatment as usual/usual care, waiting-list control). Only meta-analysis reporting between-group effect sizes were included.

Outcomes: (6) Systematic reviews had to report at least one meta-analytical result on (a) the efficacy on symptom severity or (b) treatment adherence (i.e., the degree to which a person's behavior matches with medical or health advice given by a healthcare professional or self-management treatment regime) as outcomes in children and adolescents. Furthermore, meta-regression or moderator analyses on design features and factors that are associated with the efficacy of IMIs were eligible for inclusion as well as meta-analytical comparisons of intervention components. Of note, the secondary outcome of treatment adherence was chosen, because there is some evidence that this outcome is especially important in several chronic somatic diseases (Bendig et al., 2018); other possible relevant outcomes, like level of functioning or quality of life, were not considered because of the limited space for this meta-review.

Study design: (7) Meta-analyses were based on at least three randomized controlled trials (RCTs). The majority of primary studies included in a meta-analytical comparison had to be internet based.

Publication type: (8) Eligible meta-analyses had to be written in English or German and published in a peer-reviewed journal. Narrative reviews, scoping reviews, systematic reviews without a meta-analytical quantification of effect sizes, commentaries, dissertations, or other publication types were not included.

Search Strategy, Study Selection and Data Extraction

Relevant meta-analyses were identified in March 2018 by means of a systematic literature search in the electronic databases PsycINFO and MEDLINE/PubMed with no restriction on dates of inception. The search strategy employed a combination of search terms including the target population (i.e., children or adolescents), treatment delivery (internet, online, web, digital, etc.), and type of treatment (e.g., exposure, intervention, etc.). The full list of search strings can be found in the electronic supplementary material to this article (ESM). Additionally, we scanned the reference lists of included articles. Two reviewers (MD and LS) independently reviewed the studies for inclusion or exclusion and extracted the data of eligible meta-analyses.

Quality Assessment

In order to assess the methodological quality of meta-analyses included, we applied the AMSTAR-2 checklist (Shea et al., 2017). Each included meta-analysis was assessed independently by two reviewers (MD and LS) with regard to all 16 items of the AMSTAR-2 checklist, with any disagree-

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ments discussed to reach consensus. The rating options for every item in this checklist are "Yes" and "No" as well as "Partially yes" (for items 2, 4, 7, 8, and 9), with "Yes" indicating the highest quality with regard to the respective item (Shea et al., 2017).

Results

Study Selection

The systematic literature search revealed a total of 897 records after the removal of duplicates. By screening the titles and abstracts, we identified 13 meta-analyses as potentially eligible and examined in full text review. In the end, eight meta-analyses were found to be eligible and included in this review (Ebert et al., 2015; Pai & McGrady, 2014; Pennant et al., 2015; Podina, Mogoase, David, Szentagotai, & Dobrean, 2016; Rooksby, Elouafkaoui, Humphris, Clarkson, & Freeman, 2015; Velleman, Stallard, & Richardson, 2010; Vigerland et al., 2016; Ye et al., 2014). Further details of the search process and inclusion of meta-analyses can be found in the PRISMA Flow Chart (Figure 1).

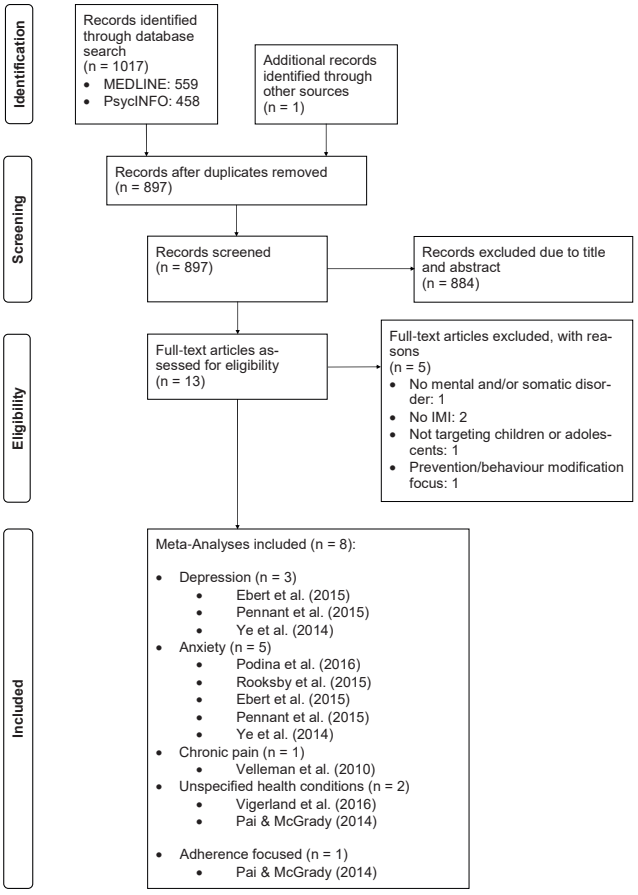


Figure 1. PRISMA Flow Chart

Characteristics of Meta-Analyses Included

The main characteristics of the meta-analyses included are summarized in Table 1. The meta-analyses were published between 2010 and 2016, with the last search dating back from March 2016 (Vigerland et al., 2016). They included 8,417 children and adolescents in total. Because most meta-analyses ($k = 5$) included studies not only limited to children and adolescents, but also incorporated studies with young adults, the age of included participants ranges between 2 and 29 years. Target diagnoses were depression ($k = 3$), anxiety ($k = 5$), chronic pain ($k = 1$), or unspecified health conditions ($k = 2$). Control conditions were nonactive ($k = 5$), face-to-face therapy ($k = 2$), a nontherapeutic control or active intervention ($k = 1$), a waiting-list control or computerized educational program ($k = 1$), and unspecified conditions like treatment as usual or education groups ($k = 1$).

Ebert et al. (2015) included interventions delivered via computer, internet, or mobile applications based on cognitive behavioral therapy (CBT) principles, whereas delivery via an internet platform was the most common type. Pennant et al. (2015) incorporated any form of computerized therapies which varied between conventional CBT approaches and dynamic gaming-type interventions. The inclusion criteria of Podina et al. (2016) covered diverse multimedia platforms (e.g., computerized or internet-delivered virtual reality [VR] environments, web conferences). Rooksby et al. (2015) summarized the results of several online and computer-assisted CBT programs. The included interventions in the meta-analysis of Velleman et al. (2010) covered CD-ROM-based and internet-based (self-help) interventions. The iCBT (internet-based cognitive behavioral therapy) definition of Vigerland et al. (2016) covered therapist-guided self-help interventions, in which a website provided content in form of texts, audio files, or videos. All interventions included in the meta-analysis of Ye et al. (2014) adhered to CBT principles and were internet and/or mobile based. In contrast to the seven symptom-focused meta-analyses mentioned above, the meta-analysis of Pai and McGrady (2014) evaluated the efficacy of online-based and conventional psychosocial interventions to promote treatment adherence.

Overall, the meta-analyses included considered a wide range of internet- and mobile-based psychosocial interventions, target diagnoses, age ranges, and control conditions; thereof, clinical heterogeneity can be considered as substantial, and we abstained from further meta-analyzing and integrating the effect sizes of the meta-analyses included.

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Table 1. Meta-analyses included concerning internet- and mobile-based interventions for mental and somatic disorders in children and adolescents.

Meta-analyses	Age range	Target diagnosis	Control conditions	No. of RCTs	Participants included	Effect size/SMD[a]	[95 % CI]
Symptom focused							
Ebert et al. (2015)	6–25 years	Depression, anxiety or both	Nonactive control condition	13	796	Overall: g = .72	.55 to .90
				7		Anxiety: g = .68	.45 to .92
				4		Depression: g = .76	.41 to 1.12
Pennant et al. (2015)	11–25 years	Risk of/diagnosed anxiety disorders or depression	Nontherapeutic control or active intervention	6	220	Anxiety: .77[b]	.09 to 1.45
				7	279	Depression: .62[b]	.11 to 1.13
Podina et al. (2016)	7–18 years	Anxiety	Waiting-list control or face-to-face treatment	6	404	vs. Waitlist-control: g = 1.4	.38 to 2.44
				8		vs. Face-to-face: g = .30	−.53 to 1.12
Rooksby et al. (2015)	7–16 years	Anxiety	Waiting-list control	5	219	.69[b]	.44 to .94
Velleman et al. (2010)	7–18 years	Chronic Pain	Waiting-list control or computerized educational program	4	150	.41[b]	.07 to .74
Vigerland et al. (2016)	3–21 years	Identified psychiatric or somatic condition (or problem)	Waiting-list control	24	1882	Overall: g = .62	.41 to .84
				11		Psychiatric: g = 1.27	.96 to 1.59
				13		Somatic: g = .49	.33 to .64
			Active control	3		vs. Active control: g = .10	−.32 to .52
			Face-to-face	3		vs. Face-to-face: g = .22	−.07 to .50
Ye et al. (2014)	7–25 years	Anxiety and depression	Waiting-list control or face-to face	7	569	vs. Waiting-list control:	
				6		• Anxiety: .52[b]	.14 to .90
				7		• Depression: .16[b]	−.12 to .44
						vs. Face-to-face:	
					2	• Anxiety: −.08[b]	−.50 to .35
					2	• Depression: 1.32[b]	−.26 to 2.90
Adherence focused							
Pai & McGrady (2014)	2–29 years	Chronic health condition	Usual care conditions, education groups and other	23	3898	Adherence:[c]	
				23		• Posttreatment: d = .20	.08 to .31
				9		• Follow-up: d = .29	.15 to .43
				6		Only web-based: d = .25	.10 to .40

Note. [a] = positive effect sizes indicate treatment effects in favor of the internet- or mobile-based intervention at posttreatment. [b] = specific method used to compute SMD was not provided. [c] = only 26.1% of the included studies were classified as web-based.

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Quality Assessment

The methodological quality of the meta-analyses included was assessed deploying the AMSTAR-2 rating scale (Shea et al., 2017). The initial accordance between the two independent reviewers (MD and LS) was close to 90 % across all meta-analyses, with discrepancies solved by discussion. The results of the quality assessment on each item can be found in Table 2. The overall quality of the meta-analyses included can be appraised as acceptable. At least half of the meta-analyses included were rated with partial to good quality ("Partial yes" or "Yes") with regard to information about PICO (participant, intervention, control condition, outcome; item 1), comprehensive literature search strategy (item 4), study selection in duplicate (item 5), data extraction in duplicate (item 6), list of excluded studies (item 7), study description in detail (item 8), risk of bias (RoB) assessment (item 9), appropriate methods for statistical combination of results (item 11), explanation and discussion of heterogeneity (item 14), and report of any potential sources of conflict of interest (item 16). The remaining items were rated as low in quality ("No") in the majority of meta-analyses included, with items 2, 3, and 10 being the least met (study protocol, explanation for the selection of study design, and report on the sources of funding for the studies included in the review).

Efficacy of IMIs for Children and Adolescents

Between-group effect sizes for IMIs in different mental disorders and somatic diseases range from SMD = .16 to 1.4 when compared to active- and nonactive controls. Most effect sizes can be classified as moderate, with effect sizes for mental disorders tending to be higher than those for somatic conditions. Cohen's *d* and Hedges' *g* were both applied in the meta-analyses included. Both statistics are denoted consistently as standardized mean differences (SMDs) in the following paragraphs; information of the actual effect size formula deployed in the respective meta-analysis can be found in Table 1.

Ebert et al. (2015) investigated the efficacy of computer- and internet-based cognitive-behavioral treatments (cCBT) for treating depression and anxiety symptoms in youth. The overall mean effect size posttest was SMD = .72 (95 % CI: .55 to .90; *s* = 13 studies), whereas cCBT was superior over nonactive controls for interventions targeting specifically anxiety (SMD = .68; 95 % CI: .45 to .92; *s* = 7) and depression (SMD = .76; 95 % CI: .41 to 1.12; s = 4) as well as for transdiagnostic treatments (SMD = .94; 95 % CI: .23 to 1.66; *s* = 2); of note, the latter meta-analytical comparison is based only on two studies. Pennant et al. (2015) also focused on anxiety and depression and found positive effects of cCBT on symptoms in young people aged between 12 and 25 years that are at risk of, or diagnosed with, anxiety disorders (SMD = .77; 95 % CI: .09 to 1.45; *s* = 6) or depression (SMD = .62; 95 % CI: .11 to 1.13; *s* = 7) when compared to active interventions or nontherapeutic control conditions. In this meta-analysis, there was no clear evidence with regard to the efficacy of IMIs in children (5–11 years) (Pennant et al., 2015). Studies investigating exclusively anxiety disorders were included in the meta-analyses of Podina et al. (2016) and Rooksby et al. (2015). Podina et al. (2016) found evidence that cognitive-behavioral therapy via electronic and technological devices or applications (eCBT) might be equally efficacious as standard cognitive-behavioral therapy (SMD = .30; 95 % CI: –.53 to 1.12; *s* = 8) and more efficacious than a waiting-list control (SMD = 1.4; 95 % CI: .38 to 2.44; *s* = 6) in children and adolescents (7–18 years). Rooksby et al. (2015) investigated the efficacy of internet-delivered CBT for pediatric anxiety disorder, and their results suggest that the programs are both comparably efficacious to clinic-based CBT when compared to waiting-list control (SMD = .69; 95 % CI: .44 to .94; *s* = 5). Velleman et al. (2010) focused on four studies on chronic pain and found evidence that children and adolescents completing a cCBT treatment are more likely to experience a posttreatment symptom reduction than those in the waiting-list control or computerized educational program control group (SMD = .41; 95 % CI: .07 to .74; *s* = 4). Vigerland et al. (2016) summarized studies investigating the efficacy of internet- and mobile-based interventions (iCBT) for identified mental or somatic conditions and found that iCBT showed superior effects when compared to waiting-list (SMD = .62; 95 % CI: .41 to .84; *s* = 24). For mental-health conditions, the effect size was SMD = 1.27 (95 % CI: .96 to 1.59; *s* = 11), with anxiety disorders being the most common mental disorder included (six studies); for somatic conditions the effect size was SMD = .49 (95 % CI: .33 to .64; *s* = 13), with pain being the most common somatic condition (five studies). When iCBT-interventions were compared to active controls in a subgroup analysis, no significant differences emerged (SMD = .10; 95 % CI: –.32 to .52; *s* = 3). However, at the same time, iCBT was not inferior when compared to conventional face-to-face CBT (SMD = .22; 95 % CI: –.07 to .50; *s* = 3). Ye et al. (2014) again concentrated on anxiety and depression. Their results showed both reduced anxiety symptom severity (SMD = .52; 95 % CI: .14 to .90; *s* = 6) and increased remission rate (pooled remission rate ratio = 3.63; 95 % CI: 1.59 to 8.27; *s* = 3) for internet-based interventions compared to waiting-list control. They found no statistically significant effect size of IMIs for

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Table 2. AMSTAR-2 Rating of included meta-analyses.

Meta-analyses	Item 1	Item 2	Item 3	Item 4	Item 5	Item 6	Item 7	Item 8	Item 9	Item 10	Item 11	Item 12	Item 13	Item 14	Item 15	Item 16
Symptom focused																
Ebert et al. (2015)	Yes	Partial yes	No	Partial yes	Yes	Yes	Yes	Partial yes	Partial yes	No	Yes	Yes	Yes	Yes	Yes	Yes
Pennant et al. (2015)	Yes	No	No	Partial yes	Yes	Yes	Yes	Partial yes	Yes	Yes	Yes	No	No	Yes	No	Yes
Podina et al. (2016)	Yes	No	No	Partial yes	Yes	No	Partial yes	Partial yes	No	No	No	No	No	Yes	Yes	Yes
Rooksby et al. (2015)	No	No	No	Partial yes	No	No	No	No	Partial yes	No	Yes	No	Yes	Yes	No	No
Velleman et al. (2010)	Yes	No	No	Partial yes	Yes	No	No	Yes	No	No	Yes	No	No	Yes	No	No
Vigerland et al. (2016)	Yes	No	Yes	Partial yes	Yes	No	Yes	No	No*	No	Yes**	No	No	Yes	Yes	Yes
Ye et al. (2014)	Yes	Partial yes	No	Partial yes	Yes	Yes	No	Yes	Yes	No	Yes	Yes	Yes	No	No	Yes
Adherence focused																
Pai & McGrady (2014)	Yes	No	Yes	Partial yes	No	Yes	Partial yes	No	Yes	No	Yes	Yes	Yes	No	No	Yes

Note. *Item 1:* Did the research questions and inclusion criteria for the review include the components of PICO? ***Item 2:*** Did the report of the review contain an explicit statement that the review methods were established prior to the conduct of the review, and did the report justify any significant deviations from the protocol? ***Item 3:*** Did the review authors explain their selection of the study designs for inclusion in the review? ***Item 4:*** Did the review authors use a comprehensive literature search strategy? ***Item 5***: Did the review authors perform study selection in duplicate? ***Item 6:*** Did the review authors perform data extraction in duplicate? ***Item 7:*** Did the review authors provide a list of excluded studies and justify the exclusions? ***Item 8:*** Did the review authors describe the included studies in adequate detail? ***Item 9:*** Did the review authors use a satisfactory technique for assessing the risk of bias (RoB) in individual studies that were included in the review? ***Item 10:*** Did the review authors report on the sources of funding for the studies included in the review? ***Item 11:*** If meta-analysis was performed, did the review authors use appropriate methods for statistical combination of results? ***Item 12:*** If meta-analysis was performed, did the review authors assess the potential impact of RoB in individual studies on the results of the meta-analysis or other evidence synthesis? ***Item 13:*** Did the review authors account for RoB in individual studies when interpreting/discussing the results of the review? ***Item 14:*** Did the review authors provide a satisfactory explanation for, and discussion of, any heterogeneity observed in the results of the review? ***Item 15:*** If they performed quantitative synthesis, did the review authors carry out an adequate investigation of publication bias (small study bias) and discuss its likely impact on the results of the review? ***Item 16:*** Did the review authors report any potential sources of conflict of interest, including any funding they received for conducting the review?; * = NRSIs (nonrandomized studies of interventions) also investigated; ** = No meta-analysis included for NRSIs (nonrandomized studies of interventions).

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anxiety when compared to face-to-face therapy (SMD = .08; 95% CI: –.35 to .50; *s* = 2); of note, this comparison was based only on two studies. For depression, no significant effect for symptom severity when compared to waiting-list control was found (SMD = .16; 95% CI: –.12 to .44; *s* = 7). Again, the comparison of IMIs vs. face-to-face therapy was based only on two studies and was nonsignificant (SMD = –1.32; 95% CI: –2.90 to .26; *s* = 2). Lastly, Pai and McGrady (2014) investigated the efficacy of online- and nononline adherence-promoting interventions for children and adolescents with chronic health conditions and found small effect sizes both at posttreatment (SMD = .20; 95% CI: .08 to .31; *s* = 23) and at follow-up (SMD = .29; 95% CI: .15 to .43; *s* = 9). The authors did not find differences between the type of intervention deliveries: Online-based interventions were as efficacious as well (SMD = .25; 95% CI: .10 to .40; *s* = 6).

Moderators and Intervention Components

Four of the eight meta-analyses included also conducted subgroup analyses to investigate sources of heterogeneity and to provide information about possible moderators. In this context, all four studies investigated the possible moderator variable age. Ebert and colleagues (2015) showed that studies aimed at adolescents achieved better results compared to those in children and mixed samples, which mirrors findings of Podina et al. (2016), who also found that older participants benefited more from IMIs for anxiety. In contrast, Vigerland et al. (2016) found no significant moderating effects of age in diverse conditions. Pennant et al. (2015) also found no moderating effects of age in studies for depression, whereas studies for anxiety showed significant moderating effects of age, in that the intervention effect was greater in studies in participants aged 18–25 years compared to those aged 12–17 years.

Participants with elevated symptom scores (undiagnosed population) showed greater effects than those with a diagnosed disorder in studies for anxiety but not in those for depression (Pennant et al., 2015).

With regard to human support, Podina et al. (2016) showed that therapist involvement (conceptualized after Newman, Szkodny, Llera, & Przeworski, 2011) significantly moderated the effect size with minimal therapist involvement yielding higher effect sizes compared to the significant therapist involvement group (e.g., additional face-to-face meetings or online patient-therapist interactions during the online intervention), whereas Pennant et al. (2015) found no moderating effect of therapist input (divided into "minimal" and "some" input) in studies for depression. Ebert et al. (2015) found no effect for parental involvement.

Vigerland et al. (2016) found moderating effects of different types of outcome ratings, with clinician ratings resulting in the highest effect sizes, whereas Pennant et al. (2015) found no effect for source of outcome assessment. Ebert et al. (2015) found no significant moderating effect of target condition or diagnosis, and Vigerland et al. (2016) found no significant effects for treatment duration.

Discussion

In this review we provided an overview of meta-analyses of internet- and mobile-based interventions for children and adolescents in various health conditions. By means of a systematic literature search, we included eight meta-analyses on different mental-health and somatic conditions in youth. Overall, we found meta-analytical evidence that IMIs achieve moderate to large effect sizes in depression and anxiety (Ebert et al., 2015; Pennant et al., 2015; Podina et al., 2016; Rooksby et al., 2015; Vigerland et al., 2016; Ye et al., 2014) and moderate effect sizes in the cotreatment of some somatic disorders (Velleman et al., 2010; Vigerland et al., 2016) when compared to nonactive controls. A finding that mirrors the meta-analytic evidence in adults (Andersson, 2016; Bendig et al., 2018), although effect sizes generally tend to be higher in adult populations. The most comprehensive meta-analytical evidence base of IMIs for children and adolescents can be found for anxiety disorders, with medium to large effect sizes, following depression with medium effect sizes, substantiated by several meta-analyses. The moderate effect size of IMIs for chronic pain is based on only one meta-analysis.

Knowledge of moderators of treatment effects in IMIs for children and adolescents is still scarce and inconsistent. In sum, three meta-analyses found evidence for the moderating effect of age (Ebert et al., 2015; Pennant et al., 2015; Podina et al., 2016), one for symptom severity (Pennant et al., 2015), and one for type of outcome assessment (Vigerland et al., 2016). Moderator analyses for age indicated that older participants achieve better results in IMIs for anxiety disorders (Ebert et al., 2015; Pennant et al., 2015; Podina et al., 2016). This is in line with previous results on IMIs (Hollis et al., 2017) and on conventional face-to-face-psychotherapy for anxiety disorders in youth (Reynolds, Wilson, Austin, & Hooper, 2012), but stands in contrast with the results of the meta-analysis of Vigerland et al. (2016), where age as moderator was nonsignificant in IMIs for various health conditions. Additionally, Pennant et al. (2015) did not find a moderating effect of age in studies for depression.

The moderating effect of disorder severity was previously shown in conventional psychotherapy (Weisz et al., 2013), which echoes the findings of Pennant et al. (2015),

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who revealed greater effects for participants with only elevated scores than for those with a diagnosed disorder in IMIs for anxiety, but not in those for depression. The previously proposed importance of parental involvement (Barrett, Dadds, & Rapee, 1996) could not be substantiated in one meta-analysis on IMIs (Ebert et al., 2015), which found no association between the inclusion of parents and better treatment outcomes. Still, in a recent meta-analysis on mobile-based apps for health behavior change in youth, Fedele and colleagues (2017) found evidence that the interventions that included caregivers produced larger effect sizes than those that did not include caregivers. As such, further research is needed to enlarge the limited evidence base and to explore the role of parental support in IMIs in more detail.

The same applies for the role of therapist support (i.e., guidance). Studies with a focus on children tended to have a higher degree of guidance than studies directed to older participants (Pennant et al., 2015; Rooksby et al., 2015). Nevertheless, all moderator analyses of therapist support were nonsignificant, despite the findings from Podina et al. (2016), where the minimal therapist involvement group revealed better outcomes than the significant therapist involvement group for anxious children and adolescents. Still, there is a large evidence base in IMIs for adults in different common mental disorders, suggesting that guided IMIs are more beneficial than completely unguided self-help interventions (Baumeister et al., 2014; von Rezori, Geßlein, Baumeister, & Domhardt, submitted). It is possible that in some anxiety disorders minimal therapist input might be sufficient to achieve clinically relevant effects, and that additional intensive guidance might be beneficial especially in patients with lower levels of motivation (Domhardt, Geßlein, von Rezori & Baumeister (in press); Newman, Erickson, Przeworski, & Dzus, 2003). The nonsignificant findings with regard to the role of guidance in most meta-analyses included in this review are probably due to the fact that the majority of examined IMIs had some degree of therapist support, which is why differentiated analyses were not possible. Furthermore, missing data on the actual therapist time invested precluded fine-grained analyses in some meta-analyses (e.g., Vigerland et al., 2016). Therefore, a standardization with regard to the degree of therapist support (e.g., Newman et al., 2011) as well as the investigation of the impact of guidance on intervention adherence in future research are worthwhile, as high attrition and drop-out rates are a common problem in IMIs.

At the moment, evidence-based knowledge on design features and intervention components for IMIs in children and adolescents is rather limited. Thus, recommendations on how to best design and adapt IMIs for youth are largely intuitive and based on practical experiences to date. This applies to the role of parental support and guidance by e-coaches, which ought to be provided in IMIs especially for children and younger adolescents. Guidance by e-coaches might be central to warranting the safety of interventions and secure, that nonresponding youth are referred to service supplies of higher intensities. The design, content, and presentation of material of IMIs should be all adapted to the age and developmental needs of the respective target group (Stasiak et al., 2016). Qualitative research designs (e.g., focus groups or think-aloud interviews) might help to detect the specific needs of children and adolescents, which could be later complemented by specific methods for the formative development of intervention packages of IMIs (e.g., Collins, Murphy, & Strecher, 2007). Furthermore, the Persuasive System Design (PSD) framework might highlight intervention components that are associated with greater user satisfaction and engagement with IMIs (such as "credibility," "dialogue support," "liking and similarity," "reduction and tunneling of therapeutic content" or "use of self-monitoring"), all contributing to improved functioning (Wozney et al., 2017). In consideration of relatively high drop-out rates, potential further acceptance- and adherence-facilitating features (such as interactive quizzes, videos, or cartoons) should be integrated in the intervention, although comprehensive empirical proof for a gamification approach and the other recommendations listed above has yet to be brought forward.

Limitations

When interpreting the findings of this meta-review, several limitations pertaining to the review itself, the meta-analyses included as well as their respective primary studies should be considered. The present systematic review of meta-analyses itself might be limited by the small number and heterogeneity of meta-analyses included as well as the omission of an a priori published study protocol. Because of the clinical heterogeneity of eligible meta-analyses, no meta-analytical integration of effect sizes of the meta-analyses was carried out. Moreover, because of the limited and inconsistent evidence base, no robust conclusions can be drawn on the critical (design) features and intervention components for this age group up to now.

The eight reviewed meta-analyses themselves are based on a limited number of primary studies (Ebert et al., 2015; Pai & McGrady, 2014; Pennant et al., 2015; Velleman et al., 2010; Vigerland et al., 2016). Furthermore, most of the meta-analyses on mental disorders were limited to anxiety and depression, and the effect sizes of IMIs were most often calculated in comparison to nonactive control groups. So far, only three meta-analyses included in the current meta-review report effect sizes for IMIs in

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comparison to face-to-face therapy based on a very low number of primary studies (Podina et al., 2016; Vigerland et al., 2016; Ye et al., 2014). Additionally, the findings have to be interpreted in the light of the heterogeneity of included primary studies regarding treatment format (Ebert et al., 2015), outcome assessment (Pennant et al., 2015; Vigerland et al., 2016), design and sample sizes (Rooksby et al., 2015), intervention duration, outcome follow-up length and baseline differences (Ye et al., 2014), and the diversity of populations and adherence targets (Pai & McGrady, 2014). Likewise, the generalizability is limited because included primary studies were most often conducted in high-income countries (e.g., Ebert et al., 2015) and participants referred themselves to the intervention or where nonsystematically selected (e.g., Rooksby et al., 2015). Overall, the quality rating of the eight meta-analyses indicated some methodological weaknesses and a comprehensive examination of different intervention components is still unresolved, in order to determine the active ingredients of IMIs.

Future Directions

We identified several important gaps in the literature that represent key areas for future research on IMIs for children and adolescents. First of all, because the meta-analyses included could only resort to a rather narrow number of primary studies, it is central to conduct further RCTs in order to enlarge the evidence base for the efficacy of IMIs, especially with regard to children and younger adolescents (≤ 12–14 years). Additionally, it is also central to further determine the long-term treatment effects of IMIs in this younger age group as well as to conduct direct comparisons of IMIs against face-to-face therapies, since only few studies provided such information. Second, integrated and meta-analytical knowledge on the cost-effectiveness of IMIs for children and adolescents is imminent and urgently needed, so that the often presumed advantage of IMIs with regard to health economic costs, scalability, and reduced therapist time can be validated and corroborated (Boydell et al., 2014; Hollis et al., 2017). Third, despite the overall importance of information on possible adverse events of IMIs, the evidence base for children and adolescents lags behind the field in adults, where comprehensive knowledge on the safety of these interventions already exists (Ebert et al., 2016; Karyotaki et al., 2018). Future studies should routinely capture the safety of IMIs and address this issue in corresponding publications, providing the opportunity to integrate knowledge in specific systematic reviews and meta-analyses. Fourth, more research on moderators is necessary to answer the question for whom IMIs work and for whom they work best. Besides the identified moderators in this review (Table 3), research on the active intervention components of IMIs in direct comparisons (i.e., dismantling or additive design studies; e.g., Borkovec & Castonguay, 1998) is worthwhile. In a similar vein, future studies on the mediators and mechanisms of change in IMIs for children and adolescents is valuable, in order to guarantee the efficacy of newly developed interventions and maximize treatment packages. Fifth, considering that most meta-analyses included are based on primary studies with clinical samples, important future directions lie in considering efficacy studies in nonclinical and general populations as well as determining the efficacy in specific populations of children and adolescents with chronic medical conditions. Finally, beside the possible advantages of IMIs outlined above, these interventions might also be prone to several constraints and special challenges, which should all be considered in future research. Among the possible limitations of IMIs are different issues such as data-safety concerns, appropriate diagnostic procedures, restricted capabilities in crises intervention, high dropout rates, and the limited knowledge on possible negative effects or contraindications to this point (for an in-depth review of the pros and cons of IMIs see Andersson & Titov, 2014).

Conclusion

This meta-review suggests that internet- and mobile-based interventions are efficacious in some (mental)-health conditions for youths, with moderate effect sizes on average. At present, the evidence base is substantiated for anxiety disorders, depression, and chronic pain – at least for the short-term, in older participants (adolescents) and when compared to waiting-list. However, because the current evidence is restricted to a rather small sample of meta-analyses based on a limited number of primary studies, and several important research questions are not (sufficiently) answered up to now, future and ongoing high-quality research is needed to comprehensively assess the potential of IMIs to improve access to evidence-based (mental) healthcare for children and adolescents.

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Table 3. Moderators and intervention components of included meta-analyses.

Meta-analyses	Significant moderators	Nonsignificant moderators	Intervention components
Symptom focused			
Ebert et al. (2015)	• Age: better results in studies aimed at older participants (adolescents)	• Target condition • Confirmation of disorder • Parental involvement • Risk of bias	–
Pennant et al. (2015)	• Age (for studies for anxiety): greater effect for older participants (same subgroups of studies as for severity) • Severity (for studies for anxiety): greater effects for studies in young people with only elevated symptom scores compared with studies of young people with diagnosed anxiety disorders	• Age (for studies for depression) • Severity (for studies for depression)	• Comparisons of ABM, CBM-I, cPST, and a mobile-phone application with nontherapeutic controls showed inconclusive findings • Therapist involvement/guidance: for studies for depression there was no conclusive difference between subgroups
Podina et al. (2016)	• Age: older participants show greater clinical benefits	• Source of anxiety assessment	• Therapist involvement/guidance: minimal therapist involvement condition most efficacious
Rooksby et al. (2015)	–	–	–
Velleman et al. (2010)	–	–	–
Vigerland et al. (2016)	• Outcome measurement: highest effect size with clinician ratings (significant higher than child self-report ratings and physiological measures); no significant difference between parent ratings and clinician ratings	• Sample size • Treatment duration • Age • Study quality	–
Ye et al. (2014)	–	–	–
Adherence focused			
Pai & McGrady (2014)		–	–

Note. ABM = Attention bias modification. CBM-I = Cognitive bias modification of interpretations. cPST = Computerized problem-solving therapy.

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Electronic Supplementary Material

The electronic supplementary material (ESM) is available with the online version of the article at doi 10.1024/1422-4917/a000625.

ESM 1. Table.
Search strings for PsycINFO and MEDLINE/Pubmed in Ovid.

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Chapter 2

Are Internet- and mobile-based interventions effective in adults with diagnosed panic disorder and/or agoraphobia? A systematic review and meta-analysis

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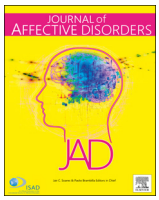
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Review article

Are Internet- and mobile-based interventions effective in adults with diagnosed panic disorder and/or agoraphobia? A systematic review and meta-analysis



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ABSTRACT

Background: There is no meta-analysis that specifically evaluates the effectiveness of Internet- and mobile-based interventions (IMIs) in adults with diagnosed panic disorder and/or agoraphobia (PD/A) so far. The current meta-analysis aims to fill this gap (PROSPERO CRD 42016034016).

Methods: Systematic literature searches in six databases for randomised and controlled clinical trials investigating IMIs in adults, who met diagnostic criteria for PD/A. Study selection and data extraction were conducted independently by two reviewers. Random-effects meta-analyses, pre-planned subgroup and sensitivity analyses were conducted when appropriate. Primary outcomes were PD and A symptom severity. In addition, adherence, response, remission, quality of life, anxiety and depression symptom severity were examined.

Results: A total of 16 trials (1015 patients), with 21 comparisons (9 IMI vs. waitlist; 7 IMI vs. IMI; 5 IMI vs. active treatment condition), were included. IMIs revealed beneficial effects on panic (Hedges' g range -2.61 to -0.25) and agoraphobia symptom severity when compared to waitlist (pooled $g = -1.15$, [95%-CI $= -1.56$; -0.74]). Studies comparing IMIs to active controls (i.e., face-to-face CBT and applied relaxation) did not find significant differences for reductions in panic ($g = -0.02$, [95%-CI $= -0.25$; 0.21]) and agoraphobia symptom severity ($g = -0.10$, [95%-CI $= -0.39$; 0.19]). Furthermore, IMIs were superior to waitlist controls regarding anxiety and depression symptom severity and quality of life.

Limitations: Tests for publication bias were not feasible due to the limited number of trials per comparison, and the risk of bias assessment indicated some methodological shortcomings.

Conclusions: Findings from this meta-analytic review provide support for the effectiveness of IMIs in patients with verified PD/A. However, before IMIs can be included in treatment guidelines for PD/A, future high quality research is needed that substantiates and extends the evidence base, especially in regard to intervention safety.

1. Introduction

Panic disorders, with and without agoraphobia (PD/A), are highly prevalent anxiety disorders (Jonge et al., 2016), which are associated with significant personal suffering (Lochner et al., 2003) and substantial disease burden (Baxter et al., 2014). Several psychological and pharmacological interventions are effective in treating PD/A (Imai et al., 2016; Pompoli et al., 2016), with psychological interventions being recommended as first line treatment in some treatment guidelines (e.g., NICE, 2019). Especially cognitive behavioural therapy (CBT) has proven its effectiveness for PD/A in several meta-analytic reviews to date (Hofmann and Smits, 2008; Cuijpers et al., 2016). However, different individual and structural access barriers lead to low uptake rates of evidence-based treatments in patients with mental disorders in general (Andrade et al., 2014), and in patients with PD/A in particular (Collins et al., 2004; Carlbring, 2006).

Internet- and mobile-based interventions (IMIs) might provide means to overcome some of these barriers, such as restricted availability of conventional face-to-face psychotherapies or perceived stigma threat (Ebert et al., 2018), given their particular features and presumed advantages, like flexibility in conduct irrespective of the constraints of space and time, as well as possible anonymity and scalability on a larger

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scale. IMIs are predominantly self-help interventions that are delivered remotely via electronic devices (e.g., computers, tablets or smartphones) and complemented by varying degrees and types of human support (Domhardt et al., 2018a). The contact between the patient and the so called *e-coach* (often a therapist or clinician) in most of these interventions is minimal and provided via asynchronous text messages, with the primary goal to increase intervention adherence (Baumeister et al., 2014). These guided interventions can be differentiated from purely unguided self-help interventions on the one hand, and conventional psychotherapy provided via video calls on the other end of the continuum (Baumeister et al., 2014).

Meanwhile, Internet interventions have been researched for over 20 years (Andersson et al., 2019) and a growing body of evidence supports their efficacy in adults with different anxiety disorder symptoms (Arnberg et al., 2014; Olthuis et al., 2016). Some meta-analytic reviews even indicate that guided Internet interventions might be as effective as conventional face-to-face therapies for patients with anxiety disorders and depression (Cuijpers et al., 2010; Carlbring et al., 2018). Thereby, research suggests that accompanying human support significantly contributes to increased effect sizes, with guided interventions consistently being more effective than unguided IMIs in different common mental disorders (Baumeister et al., 2014) and the anxiety disorders (Domhardt et al., 2018b, 2019). Furthermore, mobile-based interventions were also found to be efficacious in treating symptoms of several anxiety disorders, as indicated by some recent meta-analytical evidence (Firth et al., 2017; Linardon et al., 2019).

By now, however, there is only limited evidence on IMIs specific for adults with PD/A symptoms and this scarce knowledge is derived from subgroup analyses in reviews including various anxiety disorders so far. For example, Andrews et al. (2018) showed in subgroup analyses that Internet-based and computerised CBT was effective for panic symptoms with a large pooled effect size (Hedges' $g = 1.31$) when compared to control conditions. Similarly, Olthuis et al. (2016) documented in a Cochrane Review the efficacy of guided Internet-based CBT (iCBT) on panic disorder symptom severity with a large pooled effect size (Cohen's $d = 1.52$) when compared to waitlist, incorporating several anxiety disorders at the same time. Another recent meta-analysis investigated, if the effects of iCBT in various anxiety disorders are moderated by recruitment settings and strategies (Romijn et al., 2019). Thereby, iCBT was found to be effective in samples recruited from clinical practices on anxiety symptoms when compared to waitlist, but effect sizes were smaller than those found in studies with an open recruitment strategy and within community samples (Romijn et al., 2019).

The present systematic review and meta-analysis complements and extends the current evidence base by investigating several new aspects, which were not addressed in previous reviews to this point. First and foremost, this is the first meta-analysis exclusively focussing on clinical samples of adults that met diagnostic criteria for PD/A, according to DSM or ICD and established by a diagnostic interview. All former meta-analyses included studies in which PD/A symptom severity were based on self-reports, and diagnoses of PD/A were not consistently and validly corroborated. Second, previous reviews mingled Internet-based and computerised interventions at the same time (Andrews et al., 2018), and all meta-analyses limited therapeutic approaches to CBT (Olthuis et al., 2016; Andrews et al., 2018; Romijn et al., 2019), omitting theoretical foundations beyond CBT. Third, former meta-analyses deployed only waitlist or face-to-face treatments control conditions (Olthuis et al., 2016; Andrews et al., 2018; Romijn et al., 2019), whereas the present review included all types of controls in studies focussing on samples with a verified PD/A diagnosis. Overall, the following research questions guided the conduction of this meta-analytic review:

1) Are IMIs effective in adults with diagnosed PD/A? a) Are IMIs more effective than no-treatment and waitlist conditions? b) Are IMIs more effective than established active treatment conditions, including face-to-face psychotherapies and pharmacotherapies that are bona fide (i.e., intended to be therapeutic)? And, are IMIs more effective than active attention, psychological placebo or other non-bona fide control conditions (i.e., not intended to be therapeutic)? c) Do IMIs with various theoretical underpinnings and operationalisations differ in their effectiveness?

2) Which moderators of treatment effectiveness can be identified?

2. Methods

The design of this meta-analytic review is detailed in a pre-registered study protocol (https://osf.io/8p5jw). Further information on this study can be found with PROSPERO (CRD 42016034016).

2.1. Eligibility criteria

The current review included randomised and controlled clinical trials (RCTs/CCTs) with adults (≥ 18 years), who meet diagnostic criteria for PD/A, according to a standardised diagnostic interview based on DSM or ICD, established for instance with the SCID (The structured clinical interview for DSM-IV; First et al., 2002) or the MINI (Mini-International Neuropsychiatric Interview; Sheehan et al., 1998), or diagnosis made by a mental healthcare professional (e.g., clinical psychologist, psychotherapist or psychiatrist). Studies utilising mixed study samples (e.g., participants with social anxiety, generalised anxiety and panic disorder in one sample) or participants with clinical and subclinical PD/A symptoms in one sample were included, when the subgroup with PD/A met inclusion criteria and relevant data were reported separately for each subgroup. Samples consisting of participants with PD/A and additional comorbid diagnoses were also included. IMIs were defined as any guided or unguided psychotherapeutic intervention targeting PD/A, provided in an online or mobile setting. Interventions not reliant upon the Internet (such as computer-based interventions) or mirroring face-to-face psychotherapies via telephone/telemedicine, were not classified as Internet-based interventions and were therefore not included in the current review.

The following comparison conditions were eligible for this meta-analytic review: 1) no treatment, 2) waitlist control, 3) active treatments, such as an alternative IMI or face-to-face interventions, and 4) attention control or psychological placebo conditions. Primary outcomes were the change in panic and agoraphobia symptom severity. Secondary outcomes were treatment response and PD/A remission, adherence, dropout rate, change in quality of life, as well as anxiety and depression symptom severity. If a study contained different measures (e.g., of panic symptom severity), the following steps were carried out, to select one outcome measure for analyses: 1) external assessment/clinician rating was chosen instead of self-report; 2) more frequently used measures across eligible studies were preferred; 3) the instrument with better reliability was favoured; 4) one outcome measure was randomly chosen, in case of the aforementioned criteria were not sufficient to come to a decision. Follow-up assessments of any length were included and differentiated into short- (0 to 3 months after post-treatment), medium- (>3 to ≤6 months) and long-term (>6 months) follow-up.

2.2. Information sources

To identify eligible studies, the following steps were implemented. First, systematic searches were conducted by using a comprehensive search strategy for the electronic databases PsycINFO, PSYNDEX, Medline, EMBASE and two databases of The Cochrane Library (CENTRAL and HTA) via the search interface of Ovid (the full list of search strings for each database are outlined in the study protocol and detailed in Table A1 in the Appendix). In a second step, studies included in prior systematic reviews and meta-analyses were checked for eligibility as well. Third, manual searches of the reference lists of all studies included in the current review were conducted additionally. Finally,

forward searches (i.e., citation searches as recommended by the Cochrane Collaboration; Higgins and Green, 2011) were conducted in Web of Science, to identify other relevant articles, which had cited one of the eligible studies identified before.

2.3. Study selection

After screening titles and abstracts, the full texts of potentially eligible studies were reviewed in terms of the aforementioned inclusion criteria by two independent researchers. Possible disagreements were resolved by discussion or, if necessary, by consultation of a third reviewer.

2.4. Data extraction

Data were extracted independently by two reviewers. The following variables were extracted from each study:

1) *Study identification items*: authors, year of publication, country, bibliographic data;
2) *Study characteristics*: sample size, control group design/type, duration of follow-up, diagnostic interview used;
3) *Intervention characteristics*: design/type, therapeutic approach (e.g., CBT, psychodynamic therapies or other), duration, human support/guidance, time spent per client, as well as the nature and extent of face-to-face contacts before or during the intervention;
4) *Participants*: age, gender, comorbidities, diagnoses, medication, concurrent (non-pharmacological) therapies, prior treatment, setting;
5) *Outcomes*: mean scores (M), standard deviations (SD), group sizes, outcome instruments, response, remission, dropout rate, and adherence.

2.5. Risk of bias assessment

The methodological quality of included studies was assessed by deploying the Cochrane Collaboration's tool for assessing risk of bias (Higgins et al., 2011) on all seven criteria (i.e., random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting, and other bias) independently by two reviewers. Of note, in psychotherapy outcome research complete blinding of participants and personnel is generally not feasible (Munder and Barth, 2018) and not comparable to the opportunities of blinding in RCTs on pharmacological substances (drug-placebo trials). However, in our view, it is principally thinkable that in completely self-guided IMIs (without any human support) participants might be unaware of the intervention condition they receive. Especially when there are two active comparison conditions implemented that are either bona fide (i.e., intended to be therapeutic) or non-bona fide (i.e., intended to be non-therapeutic, like attention or psychological placebos), and these conditions are concealed so that study participants are unaware which active condition they receive (Furukawa et al., 2019). Additionally, publication bias was planned to be assessed for the primary outcomes by Egger's regression test for funnel plots (Sterne and Egger, 2005) and the trim and fill technique as proposed by Duval and Tweedie (2000a, 2000b).

2.6. Statistical analyses

Meta-analyses were performed within a random-effects model with a restricted maximum likelihood estimator (REML) to compute overall estimates of intervention effects. Effect sizes (provided as standardised mean differences (SMDs) and their 95%-CIs) were calculated, if data were continuous. SMDs for between group effects were calculated by the pooled standard deviation of the interventions and estimated by Hedges' *g*, as this parameter is less biased in small samples than Cohen's *d* (Borenstein, 2009). Furthermore, pre-post SMDs were calculated as recommended by Morris (2008), allowing for a descriptive comparison of within group effect sizes across trials and interventions. Response, remission and adherence of IMIs were calculated, if primary studies provided sufficient information for these indices.

Meta-analyses were conducted for three different comparison conditions: First, IMIs compared to waitlist or no treatment conditions ("IMI vs. WL"). Second, IMIs compared to active treatment conditions, including for example face-to-face psychotherapy delivered individually or in group format ("IMI vs. AT"). Third, IMIs compared to variations of other IMIs ("IMI vs. IMI"), differing in one (or more) specific intervention component(s), such as type of guidance (Domhardt et al., 2019). It was intended to investigate also a fourth comparison (IMI vs. attention or psychological placebo conditions), but no eligible study provided such information on comparisons with non-bona fide control conditions (Wampold et al., 1997).

If a primary study did investigate more than one IMI, the stronger one, in terms of the published effect size, was used for initial comparison to waitlist, active treatment conditions or in the case of two included IMIs to the remaining intervention. Sensitivity analyses did capture the potential bias with this procedure (see Section 2.7 – Additional analyses).

Altogether, negative effect sizes concerning symptom severity indicate a reduction in symptoms, and positive effect sizes in regard to quality of life indicate an increasing quality. In case of substantial statistical heterogeneity (I^2 greater than 60%; Higgins and Green, 2011), or in the event of high clinical or methodological heterogeneity, study results of primary studies were not pooled.

2.7. Additional analyses

Subgroup, sensitivity and meta-regression analyses were pre-specified in the study protocol (https://osf.io/8p5jw). For the subgroup analyses, sample characteristics were thought to be examined as possible effect-modifying factors (samples with PD/A vs. panic only vs. agoraphobia only; sample size; comorbidity; gender). Furthermore, intervention characteristics (type of delivery; degree of guidance; therapeutic approach) and study characteristics (randomisation, risk of bias) were intended to be used for subgroup analyses. Random-effects meta-regression was planned for the e-coach time spent per client during intervention. To test the robustness of effect sizes, two sensitivity analyses were intended: an alternative benchmark for the follow-up durations (post-randomisation vs. post-treatment), and if two or more IMIs were investigated in one trial, the least effective IMI should have been included in the effect size calculations instead of the most effective IMI.

3. Results

3.1. Study selection

The database searches on June 27th, 2019 yielded in 4262 records. The supplementary searches for relevant studies in the reference lists of other reviews and forward searches revealed four additional records. Finally, a total of 16 studies comprising 21 comparisons met the eligibility criteria and were included (Table 1). The study selection process is illustrated in a PRISMA flow chart in Fig. 1.

3.2. Study characteristics

The characteristics of eligible studies are detailed in Table 1. Overall, the 16 studies comprised a pooled sample of 1015 patients with diagnosed PD/A. Demographic variables indicated that the mean age of the sample was 37.87 years (SD = 10.51; with Klein et al. (2006) and Ivanova et al. (2016) not providing these data), and 68% of patients were female. The majority of included studies were RCTs (14 studies)

Table 1
Study characteristics.

Study Year	Disorder	Design	Sample	Intervention 1	Intervention 2	Comparison	Face-to-face contact[#]	Follow-Up	Instruments	Country
Allen et al. (2016)	PD/A	RCT	41 (GP)	iCBT plus therapist contact (*the Panic programm*)	~	waitlist	No	3 month	PHQ-9, PDSS	Australia
Bergström et al. (2010)	PD/A	RCT	~	iCBT plus therapist contact (*Mastery of your anxiety and panic*)	group CBT	~	Yes (In-person clinical interviews at pre-, post-treatment and 6-month follow-up)	6 month	MADRS, BAI, PDSS	Sweden
Carlbring et al. (2001)	PD/A	RCT	22 (GP)	iCBT plus therapist contact *	~	waitlist	No	~	MADRS, BDI, BAI, BSQ, ACQ, MIA, QOLI	Sweden
Carlbring et al. (2003)	PD/A	RCT	21 (GP)	iCBT plus therapist contact *	Internet-delivered AR	~	Yes (In-person diagnostic interview at pre-treatment)	~	BDI, BAI, BSQ, ACQ, MIA, QOLI	Sweden
Carlbring et al. (2005)	PD/A	RCT	49 (GP)	iCBT plus therapist contact *	face-to-face CBT	~	Yes (In-person diagnostic interview at pre-treatment)	6 month	MADRS, BDI, BAI, BSQ, ACQ, MIA, QOLI	Sweden
Carlbring et al. (2006)	PD/A	RCT	104 (OP)	iCBT plus therapist contact *	~	waitlist	No	12 month	MADRS, BDI, BAI, BSQ, ACQ, QOLI	Sweden
Ciuca et al. (2018)	PD	RCT	111 (GP)	iCBT plus therapsssist contact (*PAXPD*)	iCBT without therapist contact (*PAXPD*)	waitlist	No	1, 3, 6 month	PHQ-9, PDSS, ACQ	Romania
Ivanova et al. (2016)	PD	RCT	39 (GP)	ACT based Internet Therapy plus therapist contact (*The Anxiety Help*)	ACT based Internet Therapy without therapist contact (*The Anxiety Help*)	waitlist	No	12 month	PDSS	Sweden
Kiropoulos et al. (2008)	PD/A	RCT	86 (GP)	iCBT plus therapist contact (*Panic Online*)	face-to-face CBT	~	Yes (In-person pre- and post-treatment clinical interviews)	~	CR of PD/A, DASS-Dep, DASS-Anx, ASP, PDSS, BVS, ACQ, WHOQOL	Australia
Klein et al. (2006)	PD/A	RCT	55 (GP)	iCBT plus therapist contact (*Panic Online*)	manualised CBT workbook plus therapist contact	waitlist	No	3 month	CR of PD/A, DASS-Dep, DASS-Anx, PDSS, ACQ	Australia
Klein et al. (2009)	PD/A	RCT	57 (GP)	iCBT infrequent support (*Panic Online*)	iCBT frequent support (*Panic Online*)	~	No	~	CR of PD/A, DASS-Dep, DASS-Anx, ASP, PDSS, BVS, ACQ, WHOQOL	Australia
Oromendia et al. (2016)	PD/A	RCT	77 (GP)	iCBT scheduled support (*Free from Anxiety*)	iCBT non-scheduled support (*Free from Anxiety*)	waitlist	Yes (In-person diagnostic interview at pre-treatment)	6 month	BDI-II, BAI, ASI, PDSS	Spain
Pier et al. (2008)	PD	CCT	65 (GP)	iCBT supported by psychologist (*Panic Online*)	iCBT with face-to-face support by General Practitioner (*Panic Online*)	~	Partial yes (In-person interactions with General Practitioner in face-to-face support group only)	~	CR of PD/A, DASS_Dep, DASS-Anx, ASP, PDSS, CR of Agoraphobia, QOLI	Australia
Richards et al. (2006)	PD/A	RCT	32 (GP)	iCBT with stress management (*Panic Online*)	iCBT without stress management (*Panic Online*)	waitlist	No	3 month	CR of PD, DASS-Dep, DASS-Anx, ASP, PDSS, BVS, ACQ, WHOQOL	Australia
Shandley et al. (2008)	PD/A	CCT	96 (GP)	iCBT supported by psychologist (*Panic Online*)	iCBT with face-to-face support by General Practitioner (*Panic Online*)	~	Partial yes (In-person interactions with General Practitioner in face-to-face support group only)	6 month	CR of PD/A, DASS-Dep, DASS-Anx, ASP, PDSS, MIA, WHOQOL	Australia
Wims et al. (2010)	PD/A	RCT	54 (GP)	iCBT plus therapist contact (*the Panic programm*)	~	waitlist	No	1 month	PHQ-9, PDSS, BSQ, ACQ, MIA	Australia

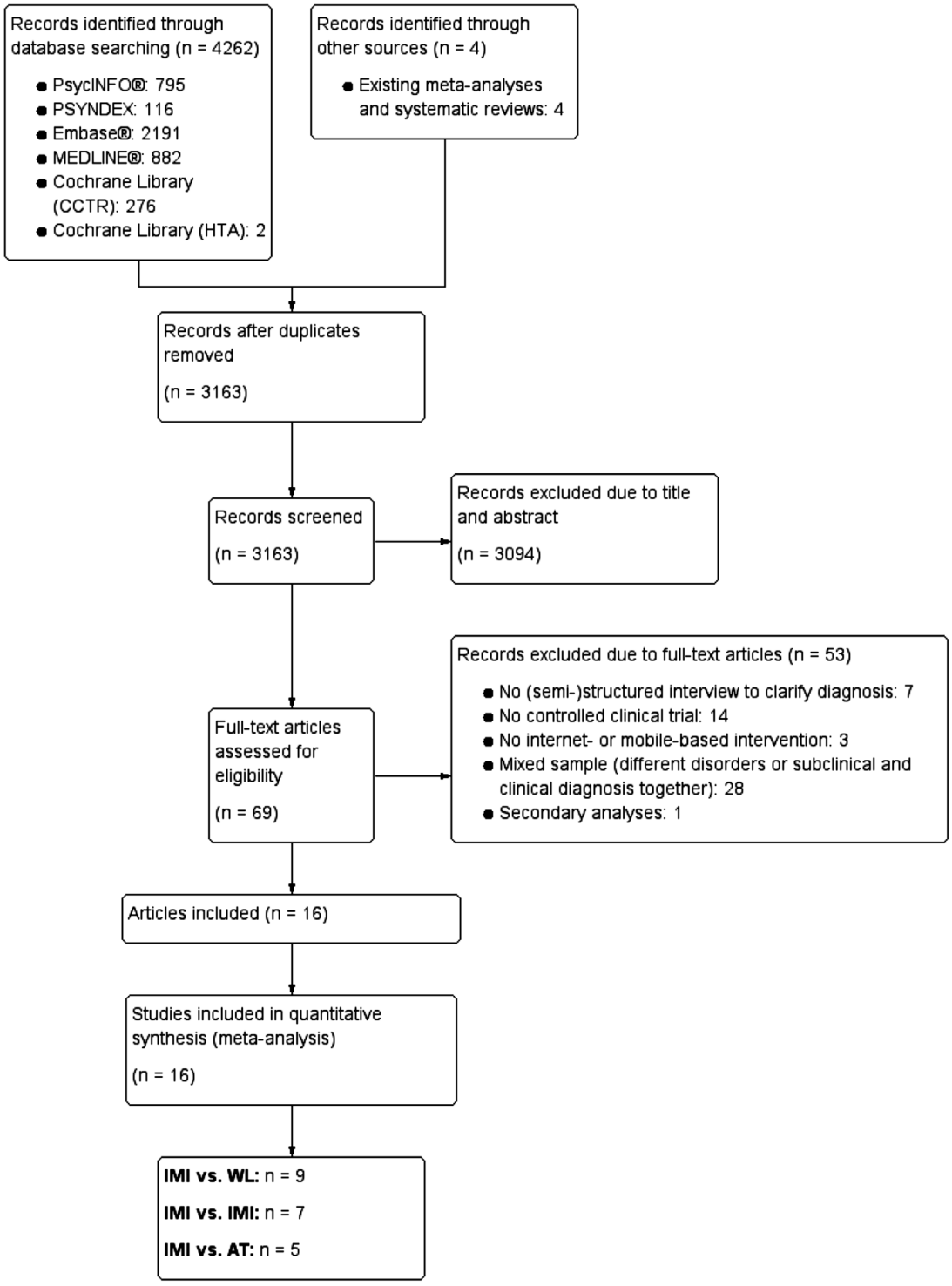


Fig. 1. Flow chart of the systematic searches and the study selection process.

and two studies were non-randomised controlled clinical trials. Thereby, nine studies compared IMIs with WL conditions, five studies compared IMIs with AT and seven studies compared IMIs with alternative IMIs. Follow-up data were provided by 11 studies: four short-term (0 to 3 months post-treatment), four medium-term (>3 to ≤6 months) and three long-term (>6 months) assessments. Studies reported results from 23 different IMIs, which consisted of 8.83 modules (SD = 3.14) and lasted for 10.61 weeks on average (range: 6–28 weeks). All IMIs were Internet-based (except the study of Ivanova et al., 2016, with an additional mobile-based component), and all but two studies investigated modularised Internet-based CBT (iCBT). Human support (i.e., guidance) was provided in 21 interventions. The average number of contacts between e-coaches and patients was 5.24 (range: 0.16–20.29) per participant and study. The total time spent by e-coaches per participant ranged from 1 to 379 min, with an average of 178 min (2.96 h) per participant.

3.3. Risk of bias assessment

Detailed information on the risk of bias assessment are provided in

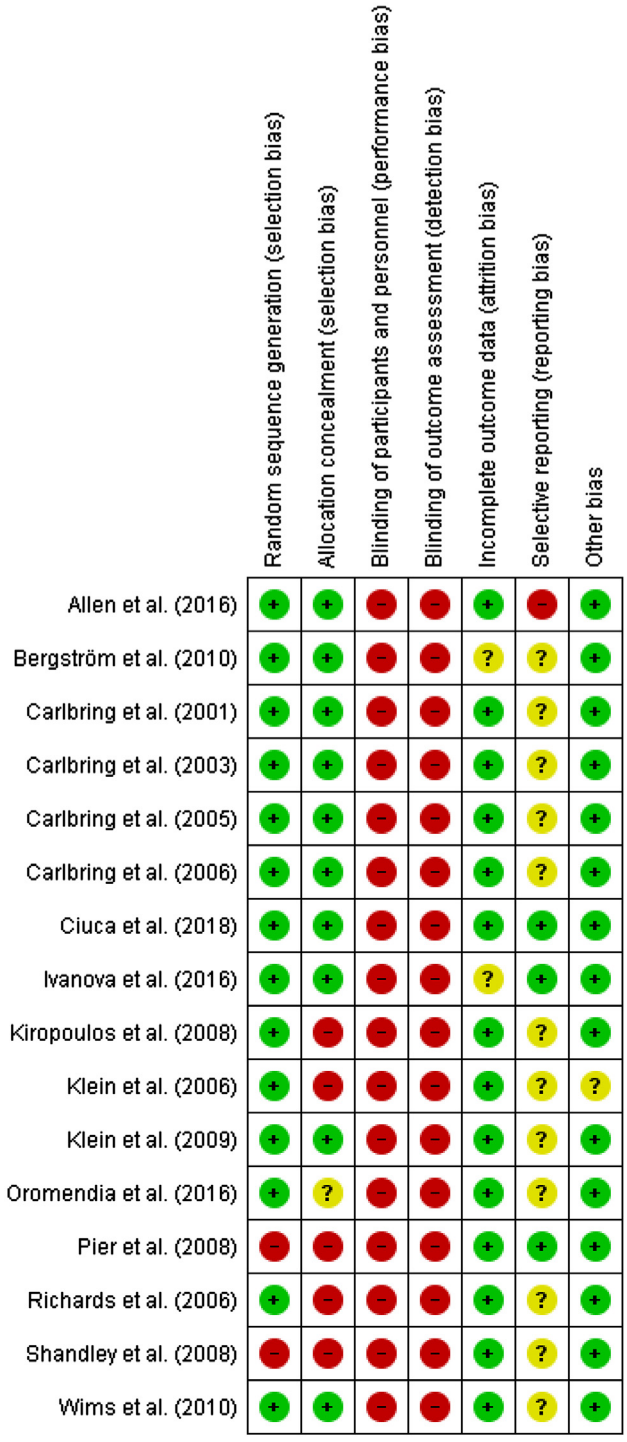


Fig. 2. Risk of bias graph review authors' judgments about each risk of bias item presented as percentages across all included studies.

Figs. 2 and 3. The criteria least met were blinding of participants and personnel, as well as blinding of outcome assessment, as all studies were rated as having a high risk of bias on these two items (as mentioned above, blinding of participants and personnel is impossible/hardly to be accomplished when investigating the efficacy and effectiveness of psychological treatments (Munder and Barth, 2018); however, blinding of participants might be theoretically achievable in RCTs on completely self-guided IMIs, when they are compared to other active bona fide or non-bona fide conditions. As no such studies were identified, we consistently rated self-reported outcome data with "high risk of bias", as participants might have been aware of the intervention condition they had received). The criterion best met over all studies was random sequence generation, as the majority of studies ($n = 14$) used an adequate method of randomisation. Overall, the methodological quality of included studies can be regarded as acceptable in the context of psychotherapeutic IMIs.

3.4. Intervention effects

3.4.1. Primary outcome: panic symptoms

IMI vs. WL: All nine studies in the IMI vs. WL (i.e., waitlist/no-treatment) comparison reported beneficial effects of interventions on panic symptom severity. Seven studies deployed waiting-list groups and two information-only-waitlists, in which participants were informed about panic disorder, but did not receive active therapy information. SMDs between interventions and waitlist groups ranged from $g = -2.61$ to -0.25 at the end of treatment (all favouring the intervention). All differences were significant, except the results of Ivanova et al. (2016; with $g = -0.25$, [95%-CI $= -1.13$; 0.63]).

The meta-analysis indicated a considerable amount of heterogeneity ($I^2 = 78.57$ %) and therefore effect sizes were not aggregated. Study-level effect-sizes and 95%-CIs are presented in Fig. 4. There were no follow-up data available, as waitlist participants received interventions directly after completion of the post-treatment assessments.

IMI vs. IMI: All seven studies in the IMI vs. IMI comparison provided data on panic symptom severity before and after the intervention (Fig. 4). Two of the seven studies found significant differences between IMIs at the end of treatment. Ciuca et al. (2018) found the intervention with therapist contact to be superior to the version without; similarly to Oromendia et al. (2016), who established a significant effect in favour of an intervention with scheduled support compared to a version with non-scheduled support. Clinical and methodological heterogeneity between studies were too high for the pooling of effect-sizes to be meaningful, as a wide range of differing components were evaluated in primary studies.

Five of seven studies provided follow-up data, three for short-, three for medium-term and one for long-term follow-up. The effects found at post-treatment, favouring interventions with more intensive guided IMIs, remained statistically significant over follow up measures up to six months after the treatment has ended.

IMI vs. AT: Within the five active treatment studies, four used face-to-face psychotherapy (individual or group CBT) as comparison condition, with no significant differences found at post-treatment (SMDs ranged from -0.48 to 0.15). The study of Carlbring et al. (2003) compared an iCBT intervention to Internet-delivered applied relaxation, with no significant difference between groups. As such, all active control conditions in this comparison can be regarded as established effective evidence-based interventions and therefore deemed bona fide. The meta-analysis indicated a non-significant overall effect of $g = -0.02$ at the end of treatment (Fig. 4). Three of five studies provided follow-up data for panic symptom severity, but differences were all non-significant at follow-up (range: $g = -0.51$ to 0.02).

Within group effect sizes: For all IMIs assessed, within group effect sizes and 95%-CIs were provided. Pre-post effect sizes for panic symptom severity ranged between $g = -2.85$ (iCBT with stress management modules and therapist contact) and -1.03 (iCBT with infrequent support). CIs indicated significant reductions for all interventions, except for the intervention investigated by Carlbring et al. (2003) yielding a within group effect size of $g = -0.76$ ($p = .0892$). Pre-follow-up results indicated significant effect sizes, ranging from $g = -3.49$ to -1.03. In contrast, within group effect sizes for waitlist controls ranged from $g = -0.61$ to 0.01 at post-treatment.

Response and remission rates: It was planned to adhere to a distribution-based method for defining responder-thresholds (the percentages of participants that reached a reduction of 0.5 standard deviations on a primary outcome measure). However, due to the heterogeneous

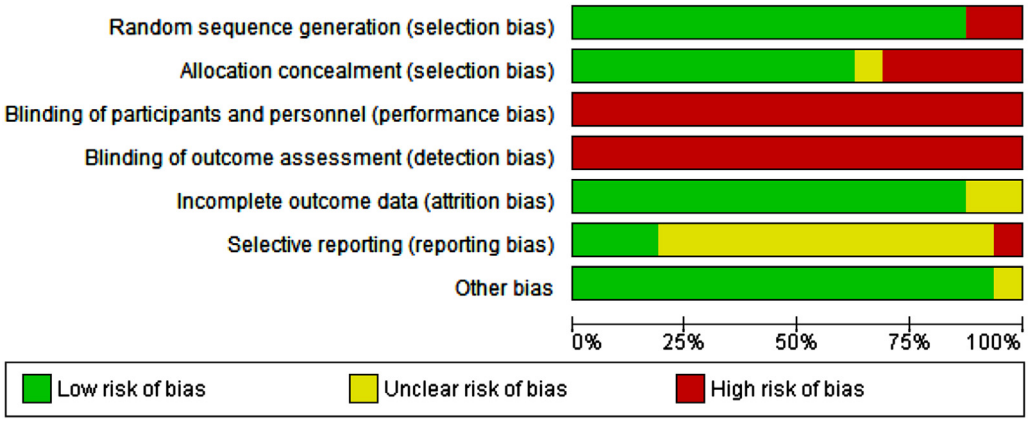


Fig. 3. Risk of bias summary review authors' judgments about each risk of bias item for each included study.

operationalisations of response and remission we withstood from aggregating the results, as additionally the estimation of missing values would have been based on too few data. Therefore, response and remission rates were reported as defined in the primary studies. The distinct response and remission rates in single studies, as well as the study-specific definitions of these indices can be found in Table A2 in the Appendix.

Response rates (or related results) were reported in six studies. The

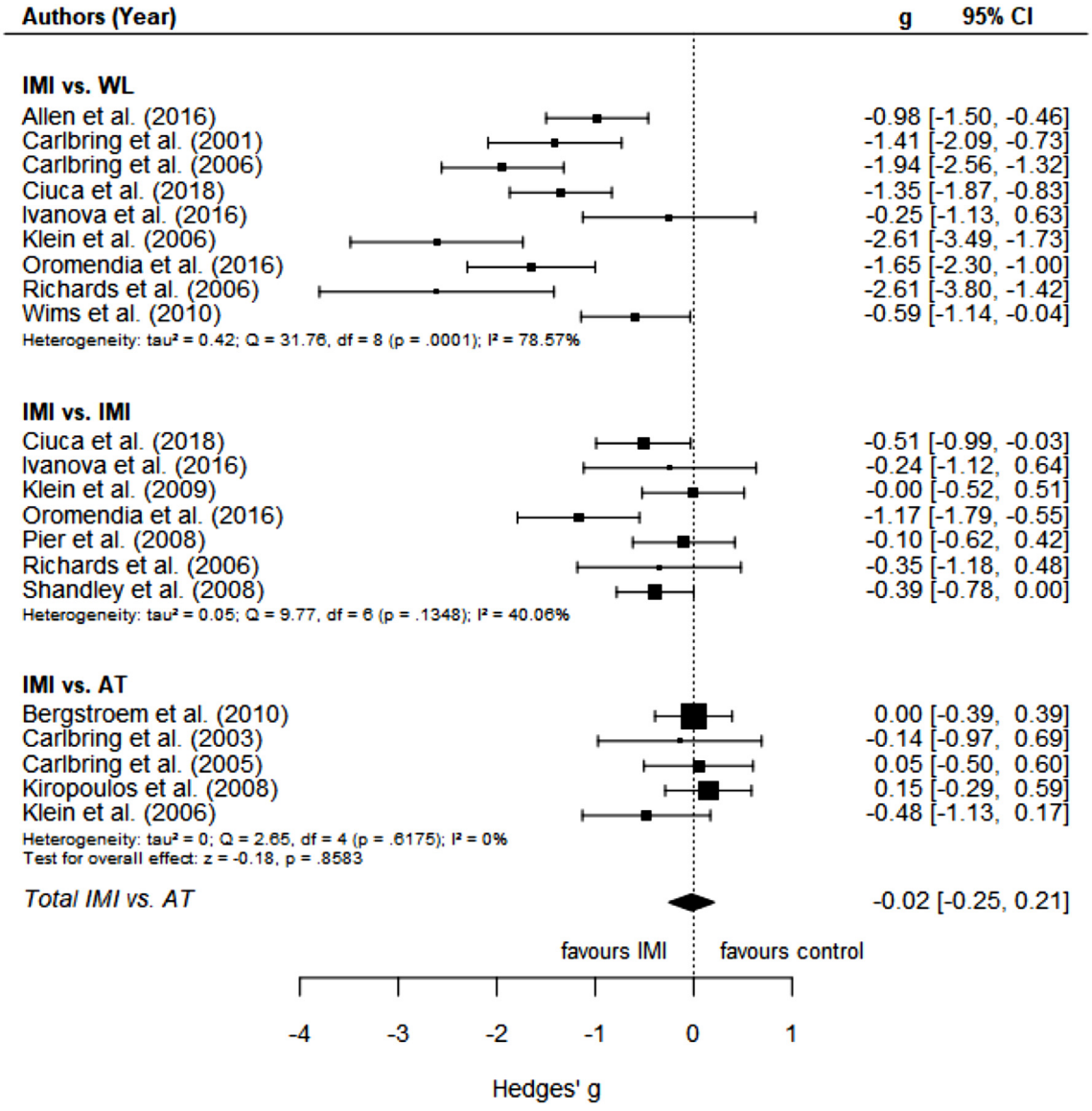


Fig. 4. Panic symptoms between intervention and comparison groups at post-treatment.

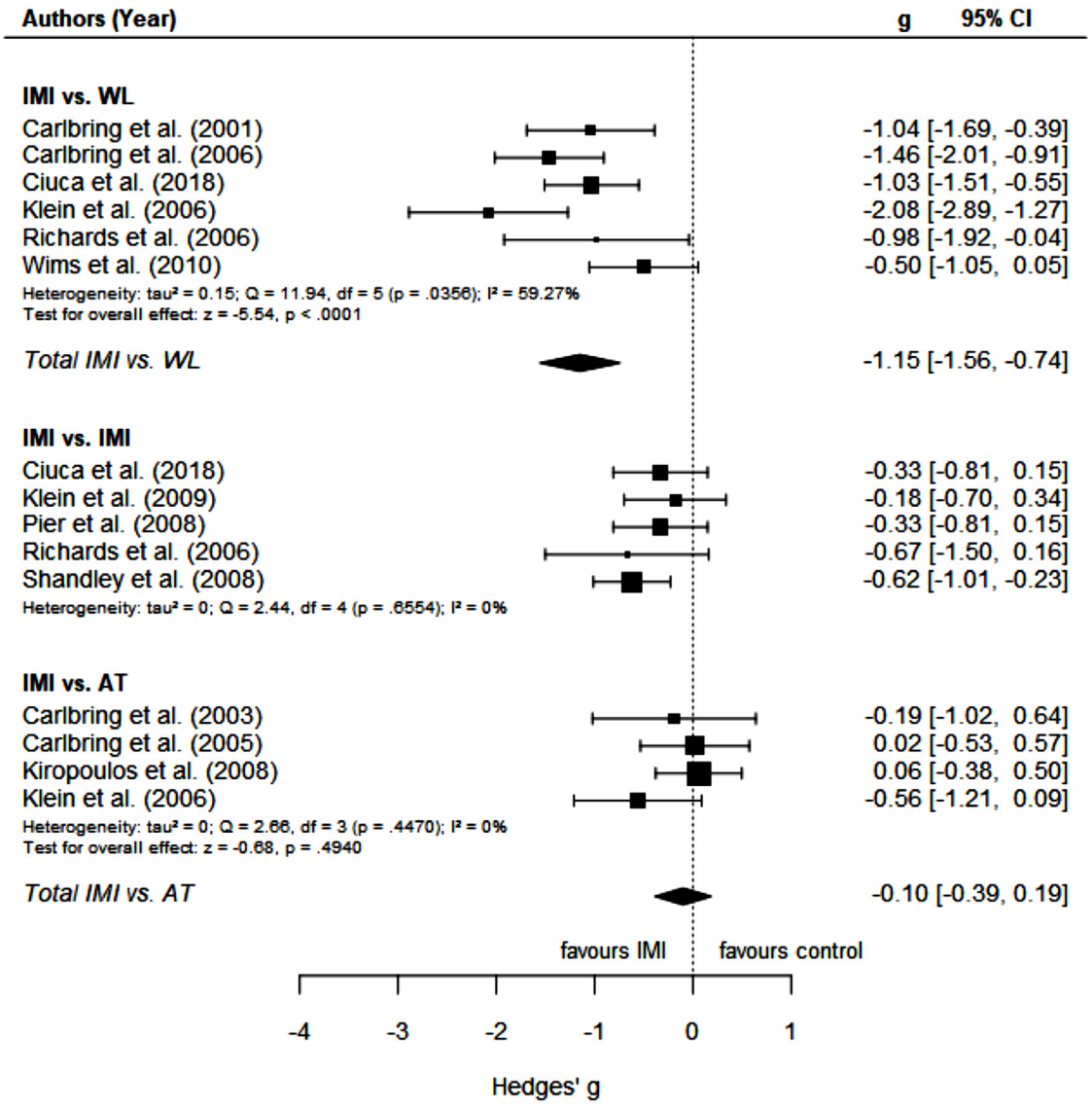


Fig. 5. Agoraphobia symptoms between intervention and comparison groups at the end of treatment.

actual response rates at post-treatment ranged from 21% (defined as the reliable change after Jacobson and Truax, 1991, on the PDSS-SR in an IMI with non-scheduled support) to 87% (corresponding to a score of less than 4 on the nine-point clinician rating Scale of the ADIS-IV; Brown et al., 1994). Remission rates have been reported in 14 out of 16 studies. Remission rates at posttreatment ranged from 26% (defined as high end-state functioning; see Brown and Barlow, 1995, and Öst and Westling, 1995; in two studies investigating IMIs with either support by a general practitioner or a psychologist) to 92% (one week panic free) in an IMI with added stress management modules. At follow-up remission rates increased, ranging from 32% to 92%.

3.4.2. Primary outcome: agoraphobia symptoms

IMI vs. WL: Six studies reported effects of the intervention on agoraphobia symptom severity. As reported in Fig. 5, the meta-analytical evaluation indicated a beneficial effect of $g = -1.15$ (95%-CI $= -1.56; -0.74$) and substantial between study heterogeneity ($I^2 = 59.27\%$). Effect sizes ranged from $g = -2.08$ to -0.50 at the end of treatment. Differences were significant in all but one study (Wims et al., 2010), all favouring intervention groups.

IMI vs. IMI: Five out of seven studies conducted an IMI versus IMI comparison and provided data on agoraphobia symptom severity (Fig. 5). Pooling of effect-sizes was not feasible due to high clinical and methodological heterogeneity.

IMI vs. AT: The meta-analysis on studies that compared the IMI to active control conditions revealed a non-significant pooled effect of $g = -0.10$ (95%-CI $= -0.39; 0.19$) at the end of treatment (see Fig. 5). Two of four studies provided follow-up data, indicating no significant differences.

Within group effect sizes: Pre-post effect sizes for agoraphobia symptom severity were calculated in 17 interventions that reported agoraphobia symptom severity and ranged between $g = -2.02$ (iCBT with support from psychologists) and -0.51 (iCBT supported by psychologists). CIs indicated significant reductions for 13 interventions, four were non-significant. Pre-follow-up effect sizes were calculated for ten intervention groups with a range from $g = -2.34$ (iCBT with therapist contact) to -0.47 (iCBT with therapist contact). Eight of ten studies indicated significant symptom reductions. Within group effect sizes for waitlist-controls ranged from $g = -0.21$ to -0.06.

Response rates: Response rates based on agoraphobia-specific measures were reported in 3 of 16 studies. Response rates ranged from 67% to 81%. At follow-up only one study reported a response rate of 67% at 12-month follow up. Thereby, all three studies were conducted by the same Swedish group (Carlbring et al., 2001, 2005, 2006), and response

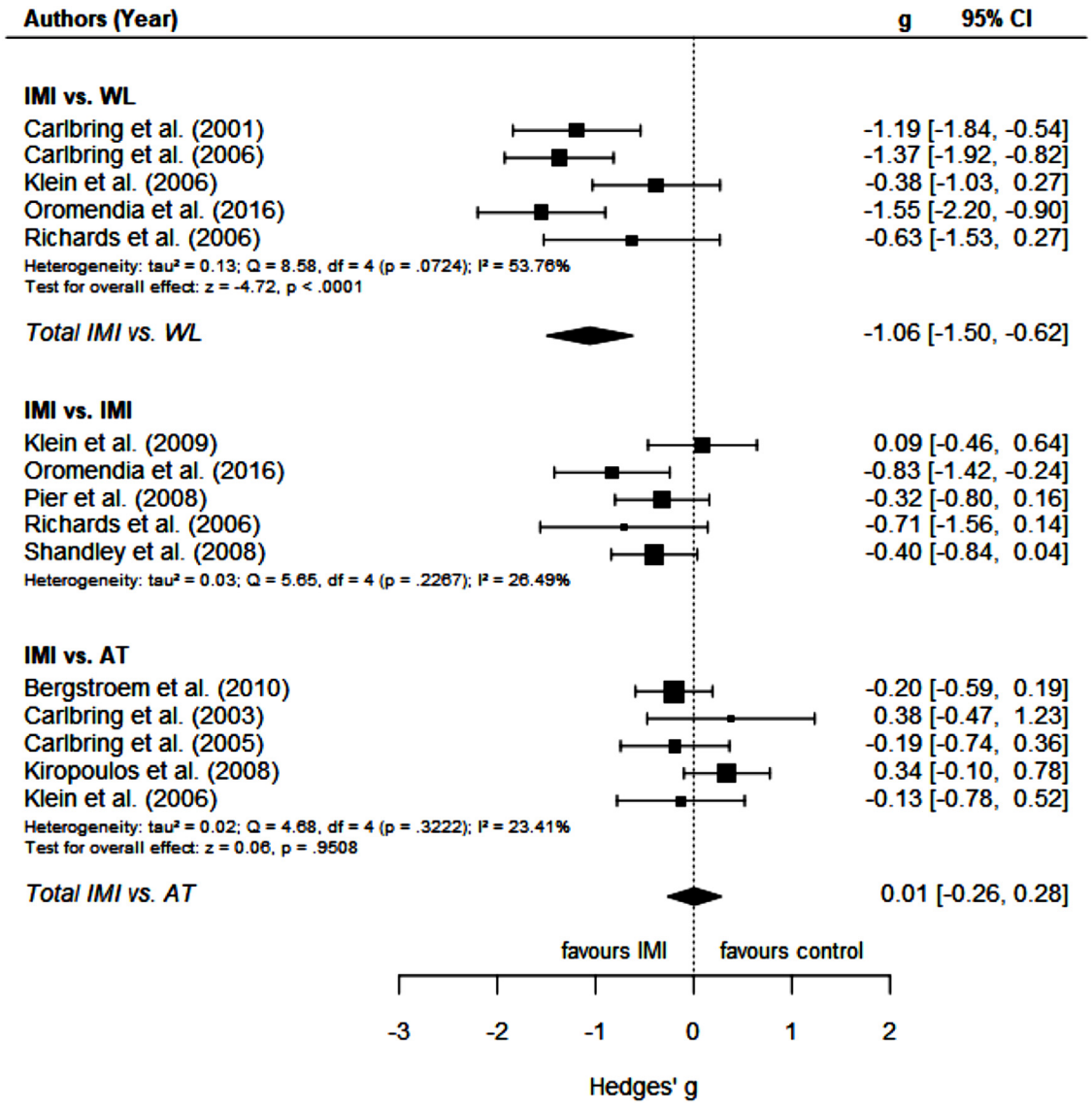


Fig. 6. Anxiety symptoms between intervention and comparison groups at the end of treatment.

was defined as reliable change after Jacobson and Truax (1991) on the ACQ (Chambless et al., 1984). Detailed information on response rates for agoraphobia-specific measures are provided in Table A2 in the Appendix.

3.4.3. Secondary outcome: anxiety symptoms

IMI vs. WL: Five studies in the IMI vs. waitlist comparison reported effects on general anxiety symptoms, aside from panic and agoraphobia. SMDs ranged from $g = -1.55$ to -0.38 at the end of treatment. Differences were significant in three of five studies, favouring the intervention. In the studies of Klein et al. (2006) and Richards et al. (2006) no significant differences were found (Fig. 6). A meta-analysis indicated a pooled effect size of $g = -1.06$ (95%-CI = -1.50; -0.62), with considerable between study heterogeneity ($I^2 = 53.76\%$).

IMI vs. IMI: Five of seven studies in the IMI vs. IMI comparison provided data on anxiety symptoms (Fig. 6). Four studies did not find a significant difference between the IMIs, while Oromendia et al. (2016) found a significant effect size of $g = -0.83$ (95%-CI = -1.42; -0.24), favouring the examined iCBT with scheduled support. Three studies provided follow-up data, of which only Oromendia et al. (2016) reported a significant effect size favouring the iCBT with scheduled support ($g = -0.71$, [95%-CI = -1.30; -0.12]).

IMI vs. AT: The five studies in the IMI vs. AT comparison did not find significant differences between the anxiety symptoms at the end of treatment. Three of five studies in the IMI vs. AT group provided follow-up data and did not find significant differences. The pooled effect-size on the comparison of IMIs to other active treatments was not significant ($g = 0.01$, [95%-CI = -0.26; 0.28]; Fig. 6).

3.4.4. Secondary outcome: depression symptoms

IMI vs. WL: Eight of nine studies in the IMI vs. waitlist comparison reported effects on depression symptom severity. Differences between groups were significant in five, and non-significant in three studies. Hedges' g ranged between -1.42 and -0.38 (Fig. 7). A pooled effect size of $g = -0.82$ (95%-CI = -1.06; -0.57), favouring the interventions was calculated, with moderate between study heterogeneity ($I^2 = 26.46\%$).

IMI vs. IMI: Six of seven studies in the IMI vs. IMI comparison reported data on depression symptoms (Fig. 7). One study found a significant difference favouring the intervention with additional support provided by psychologists over the IMI with guidance from general practitioners (Shandley et al., 2008). The other studies did not find significant effects. Effect sizes ranged from $g = -0.78$ to 0.17. Four

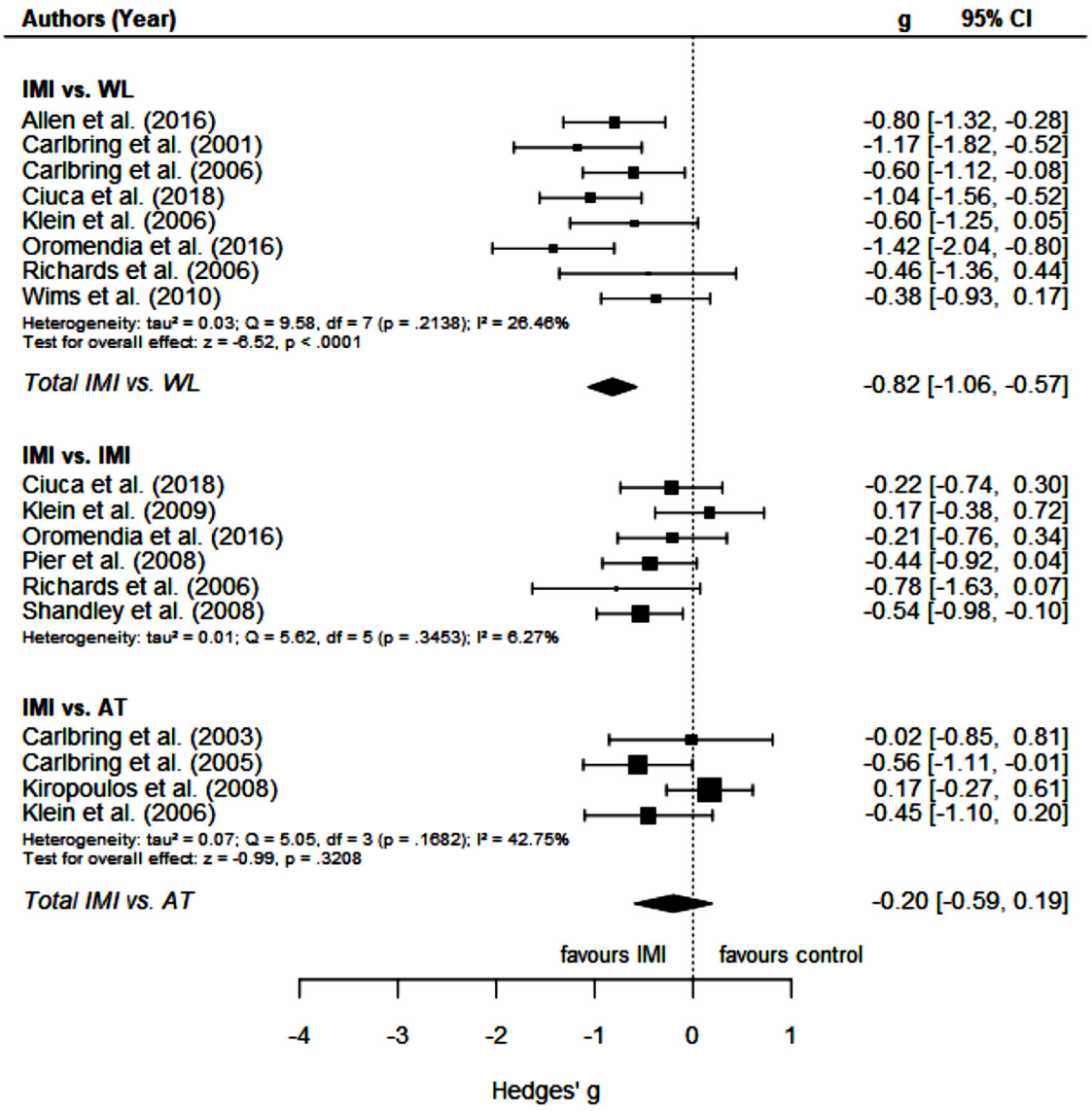


Fig. 7. Depression symptoms between intervention and comparison groups at the end of treatment.

studies provided follow-up data, with Shandley et al. (2008) reporting a similar effect as at post-treatment, and Ciuca et al. (2018) indicating a similar long-term effect on depression symptom severity as in agoraphobia: The difference between the guided vs. the unguided IMI did not show at post-treatment, but was statistically significant at one and six month follow up ($g = -0.95$ [95%-CI = −1.50; −0.40] and −0.76 [95%-CI = −1.28; −0.24]).

IMI vs. AT: Four of the five studies in the IMI vs. AT comparison reported on depressive symptom severity as outcome (Fig. 7). Carlbring et al. (2005) found the iCBT to be superior to the face-to-face CBT at post-treatment ($g = -0.56$, [95%-CI = −1.11; −0.01]. No significant differences have been found in the follow up measurements. The pooled effect was non-significant (Fig. 7). Notable, all active control conditions in this comparison can be regarded as bona fide and as established effective evidence-based interventions.

3.4.5. Secondary outcome: quality of life

IMI vs. WL: Three studies in the IMI vs. waitlist comparison reported effects on quality of life, whereas six did not. Carlbring et al. (2001) revealed a significant difference of $g = 0.74$ (95%-CI = 0.12; 1.36) favouring the intervention, the other studies did not find significant intervention effects on quality of life (Fig. 8). A meta-analysis of the studies indicated a pooled effect size of $g = 0.52$ (95%-CI = 16; 0.89) with no statistical heterogeneity ($I^2 = 0\%$).

IMI vs. IMI: Effects of different IMIs on quality of life were investigated by five studies (Fig. 8). Shandley et al. (2008) as well as Pier et al. (2008) reported a significant difference favouring the IMIs guided by psychologists over the IMIs supported by general practitioners. The remaining studies did not find significant differences. Effect sizes ranged from g = -0.22 to 0.58. Two studies provided follow-up data: Shandley et al. (2008) found a significant between group effect size at medium-term follow-up favouring the same IMI as at post-treatment, while Richards et al. (2006) did not find a significant effect.

IMI vs. AT: Three of seven studies in the IMI vs. AT comparison reported data on quality of life (Fig. 8). No study found a significant difference at the end of treatment. Only Carlbring et al. (2005) provided follow-up data and reported a non-significant finding.

3.5. Adherence and dropouts

The number of participants that completed the interventions was extracted from all 16 studies. On average, 79% of the participants completed the interventions (range: 50% to 95%). Furthermore, participants completed on average 77% of the offered modules (range: 44%

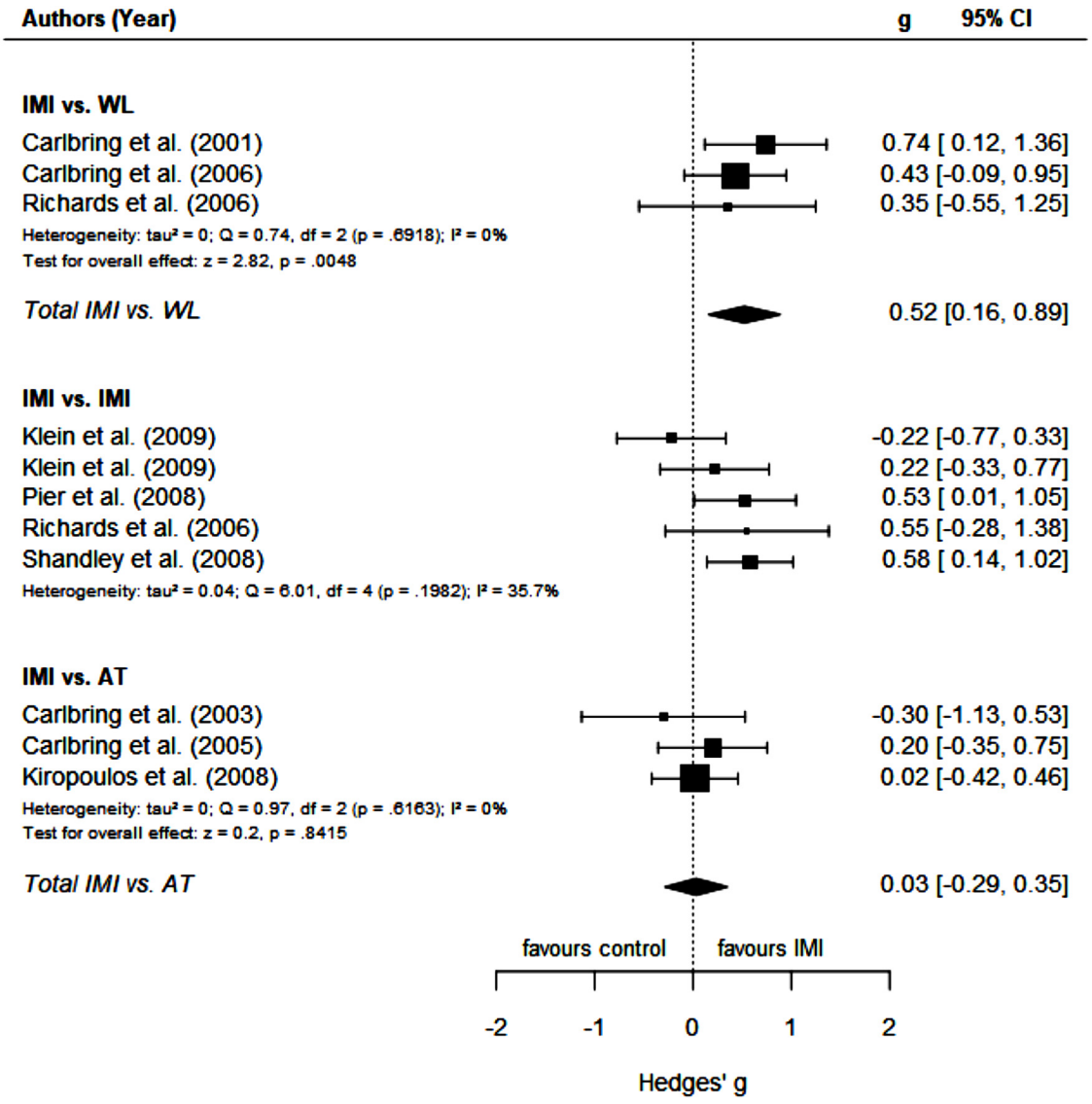


Fig. 8. Quality of life between intervention and comparison groups at the end of treatment.

to 100%). Participants who did not complete the intervention were considered as intervention dropouts. The average intervention dropout rate across studies was 21% (range: 5% to 50%).

A study dropout rate was calculated for each experimental group, defined as the number of persons who did not provide data at post-treatment or at a follow-up. On average, 18% of participants dropped out at post-treatment (range: 0% to 50%, $k = 16$ studies) and 31% dropped out at follow-up (range: 5% to 68%, $k = 11$). For the waitlist groups an average dropout rate of 15% was found (range: 3% to 29 %, $k = 8$). Over the five active treatment conditions, the average rate was 12% at post-treatment and 18% at follow-up.

3.6. Publication bias

It was planned to assess publication bias by evaluating funnel plots of SMDs in the individual comparison groups and to apply the trim and fill technique. These analyses were not feasible given the small number of included trials per comparison though (Sterne et al., 2011).

3.7. Subgroup and sensitivity analyses

Subgroup analyses to determine the impact of several variables were planned, but not feasible because of the limited number of studies per subgroup and comparison. A meta-regression for the e-coach guidance time spent per client during the interventions showed a non-significant effect on intervention outcomes, which might be due to limited variability in time spent per client, resulting from only taking the stronger IMI into the calculation. Changing the baseline for the follow-up duration did not change the categorization of studies, therefore, the planned analysis of sensitivity was not conducted here. A meta-analysis with the least effective IMI within a study did not reveal significant differences in results (IMI vs. AT in panic symptom severity: $g = -0.02$ and IMI vs. WL in agoraphobia symptom severity: $g = -0.97$).

4. Discussion

To our knowledge, this is the first systematic review that synthesized and meta-analytically evaluated the available evidence on the effectiveness of IMIs for patients with a validated diagnosis of PD/A. The results highlight that IMIs are effective in reducing panic and agoraphobia symptom severity in adults with diagnosed PD/A, with substantial effect sizes when compared to waitlist controls. Furthermore, IMIs were similar effective when compared to active

treatment conditions that are deemed to be bona fide. Altogether, in this meta-analysis of 16 trials, IMIs for PD/A evinced rather high adherence rates, and interventions were also significantly superior than waitlist conditions on the secondary outcomes depression and general anxiety symptom severity, as well as quality of life, with large to medium effect sizes, respectively.

Therewith, the results of this current meta-analysis are consistent with findings from previous research (Olthuis et al., 2016; Andrews et al., 2018), as all three reviews demonstrated the superiority of IMIs over waitlist controls with large effect sizes across intervention types. However, the findings of the present review add to prior knowledge, in that the large effect sizes are established in samples with clinically verified PD/A diagnoses only; thereby suggesting that IMIs can be conceived as an effective treatment option – next to well-established face-to-face psychotherapies and pharmacological treatment approaches (Hofmann and Smits, 2008; Cuijpers et al., 2016; Imai et al., 2016; Pompoli et al., 2016). Consequentially, future revisions of treatment guidelines might consider IMIs as an evidence-based treatment for patients with PD/A. This is also because IMIs were found similar effective than active bona fide treatment conditions (e.g., Wampold et al., 1997) in this current review. However, forthcoming studies need to extend these findings in trials specifically designed to establish the non-inferiority and equivalence of IMIs to empirically-supported face-to-face psychotherapies, with more rigorous methodological quality. Moreover and of utmost importance, future high quality research must carefully gather information on possible negative effects and deterioration rates, as this knowledge is largely pending to date, but is indispensable for a comprehensive evaluation of these rather novel technology-delivered interventions (e.g., Rozental et al., 2014; Ebert et al., 2016; Karyotaki et al., 2018). On that account, stakeholders and health care policy makers need to weigh the recent findings, together with upcoming research that endorses the safety of the interventions, recognises patient preferences and establishes a regulatory framework for their implementation in routine clinical care (Baumeister et al., 2014, 2015; Ebert et al., 2015, 2018).

Notably, the current review revealed a large beneficial effect of PD/A-specific interventions on the secondary outcomes depression and general anxiety symptom severity. Thereby, PD/A-specific IMIs seem to be even comparably effective in lowering patients` depression symptom burden as it has been documented for depression-specific IMIs in patients with verified diagnoses of major depression and/or dysthymia (Königbauer et al., 2017). This finding might stem from reductions in depressive symptoms that are caused by PD/A-burden and therefore can be considered as a “byproduct” of effective PD/A-treatments. However, it might be otherwise that interventions for depression and anxiety are to some degree compatible, or even interchangeable. Similarly, prior research has revealed that transdiagnostic IMIs are comparable effective than disorder-specific approaches for anxiety disorders in general (Domhardt et al., 2019). Thus, future research that examines generic and overarching treatment options in more detail is of high relevance, as these transdiagnostic interventions might further amplify the potential of digital health interventions for scalability purposes (Domhardt et al., 2019; Weisel et al., 2019).

All of the trials included in the present review examined guided interventions, which are known to improve patients` intervention adherence and concomitantly improve intervention outcomes (Baumeister et al., 2014; Domhardt et al., 2019). Thus, the comparably high adherence rate with an average of 78% intervention completers is not so much astonishing. This completer rate is close to the findings of Christensen et al. (2009), who reported adherence rates between 80% and 100% for guided PD interventions. In regard to a possible dose-response relationship between guidance and effectiveness, however, the random-effects meta-regression with guidance time spent per client as a predictor did not reveal a significant effect. This might suggest that the amount of guidance does not influence the beneficial effect of an intervention on panic or agoraphobia symptoms. However, as the majority of the interventions reported very similar guidance times (three outliers with substantially lower minutes spent) and the statistical power of this analysis is rather limited, this preliminary result needs to be interpreted attentively and warrants future research (Baumeister et al., 2014; Domhardt et al., 2019). Furthermore, in two studies (Pier et al., 2008; Shandley et al., 2008) human support was provided face-to-face, requiring patients to leave home for the appointments and consequently receiving higher doses of exposure – at least potentially. Likewise, in other studies patients needed to attend to in-person clinical interviews on site, in order to participate in the respective study (Bergström et al., 2010; Carlbring et al., 2003, 2005; Kiropolous et al., 2008; Oromendia et al., 2016), possibly dividing patients in those who were willing to go out, from those who were not. As such, the extent and nature of mandatory face-to-face contacts in digital health interventions for PD/A might be an important effect moderator, justifying further in-depth analyses, since exposure is well-established to be one of the most important intervention components in psychotherapies for anxiety disorders overall (Hofmann and Smits, 2008).

There are several methodological considerations and limitations concerning the included primary studies that contextualise the findings of the present review. First, the samples investigated in eligible studies differed in regard to PD/A severity, as well as in terms of the presence and severity of comorbid pathologies. Because of the somewhat heterogeneous samples and the absence of studies investigating agoraphobic patients without panic disorder, it was not possible to evaluate the effects of interventions in homogeneous and diagnosis-specific subgroups. However, as multi-comorbidity is the rule rather than the exception in clinical practices (Tully et al., 2014; Kessler et al., 2006), this aspect argues for the notion of a high external validity and generalizability of the examined clinical trials. Second, the results in regard to change in agoraphobia, anxiety and depression symptom severity should be interpreted with caution, because it is unclear how many participants fulfilled diagnostic criteria for these comorbidities, and the sample sizes were rather small. Furthermore, participants in the eligible studies were predominantly self-referred, and thus, it might be that these persons differed from those patients utilising conventional face-to-face psychotherapies in certain aspects. Third, the generalizability of the findings of eligible studies might be further reduced, since most of included trials were conducted in Australia ($k = 8$; 50%) and Sweden ($k = 6$; 37.5%). Finally and most importantly, the methodological quality of included studies can be regarded as rather frail on average, and future studies need to stick to more rigorous methodological standards, especially in terms of an appropriate allocation concealment and blinding.

Aside several strengths (i.e., compliance with a pre-registered protocol, as well as the comprehensive incorporation of IMIs with various theoretical underpinnings and formats), several methodological aspects and limitations of the meta-analysis should be mentioned. First, there were no unpublished data included in the analyses, and thus, publication bias might have led to an overestimation of effect sizes. However, trial registration seems to be widespread in this branch of research and might have lessened the chance that unpublished studies have been overlooked. Second, only studies published in English language were included. Therefore, language bias may have led to an overestimation of effects as well, as statistically significant results are more likely to be published in English (Egger et al., 1997). Third, due to the limited amount of primary studies, tests for publication bias were not doable. Fourth, the IMI vs. IMI comparisons were not based on a priori hypotheses and were exploratory in nature. Finally, several intended subgroup and moderator analyses were not feasible, as the limited amount of studies per subgroup and comparison prevented detailed investigations on possible effect-modifying variables.

5. Conclusions

Overall, the results of this meta-analytical review indicate that IMIs are more effective in reducing symptoms of panic disorder and agoraphobia than waitlist-conditions in adults with a verified diagnosis of PD/A. As such, IMIs might represent an alternative treatment for PD/A, which entail the potential to extend the reach of evidence-based treatments given their particular features and advantages, like flexibility and anonymity in conduct, as well as independence from space and time. Furthermore, IMIs seem comparably effective than active controls, whereas upcoming research must substantiate these findings in trials specifically designed to establish the non-inferiority compared to well-established face-to-face treatments like CBT. Moreover, forthcoming studies need to gather crucial information on possible adverse events and deterioration rates in IMIs for PD/A, as comprehensive knowledge on this issue is pendant. To conclude, the results from this meta-analysis provide further support for the effectiveness of IMIs in patients with PD/A, implicating that the inclusion of IMIs as an evidence-based intervention in treatment guidelines for PD/A is a viable future direction, although more high quality research is needed, to substantiate these findings with more solid evidence.

Declaration of Competing Interest

All authors declare that they have no conflicts of interest.

Declaration of Competing Interest

Availability of data: All data are available upon reasonable request from the corresponding author.

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Authors contributions

MD, JL, JKy, JKo, PD, and HB contributed to the design of the study. JL, JKo, JKy and MD conducted the systematic literature searches, extracted the data, and rated the risk of bias of included studies. JL, JKy and MD analysed the data, with statistical advice by PD. MD and JL wrote the first draft of the manuscript. All authors (MD, JL, JKy, JKo, PD, and HB) have contributed to the further writing, and have approved the final manuscript.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.jad.2020.06.059.

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Chapter 3

Efficacy of digital health interventions in youth with chronic medical conditions: A meta-analysis

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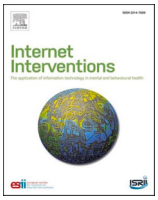
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Efficacy of digital health interventions in youth with chronic medical conditions: A meta-analysis

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ABSTRACT

Background: Digital health interventions might extend service provisions for youth with chronic medical conditions (CC) and comorbid mental health symptoms. We aimed to comprehensively evaluate the efficacy of Internet- and mobile-based interventions (IMIs) for different psychological and disease-related outcomes in children and adolescents with CC.

Method: Studies were identified by systematic searches in CENTRAL, Embase, MEDLINE/PubMed and PsycINFO, complemented by searches in reference lists of eligible studies and other reviews. We included studies, when they were randomized controlled trials (RCTs) comparing the efficacy of an IMI to control conditions in improving psychological and disease-related outcomes in youth (mean age $\leq$ 18 years) with CC. Study selection, data extraction and risk of bias assessment were conducted independently by two reviewers. Meta-analyses were performed within a random-effects model, and Hedges' g (with 95% confidence intervals) was calculated as effect size measure. Primary outcomes were comorbid mental health symptoms (i.e., depression, anxiety and stress), as well as quality of life and self-efficacy.

Results: A total of 19 randomized controlled trials (2410 patients) were included in this meta-analysis. IMIs were associated with improvements in self-efficacy ($g = 0.38$; 95% CI, 0.15 to 0.61; $I^2 = 0$) and combined disease-related outcomes ($g = -0.13$; 95% CI, −0.25 to −0.01; $I^2 = 21$). Meta-analyses on other outcomes were non-significant, and some pre-planned analyses were not feasible because of a shortage of studies.

Conclusion: The available evidence on IMIs for improving mental and health-related outcomes in youth with CC is limited. Our findings point to a rather small benefit and limited efficacy. Future research is needed, to comprehensively assess the potential of IMIs to extend collaborative care, and to identify factors contributing to improved user-centered interventions with better treatment outcomes.

1. Introduction

Chronic medical conditions (CC) in children and adolescents are highly prevalent (van der Lee et al., 2007), and are associated with substantial personal suffering and disease burden worldwide (WHO, 2018). These medical conditions comprise a range of different disorders, including diabetes, respiratory diseases or chronic pain (WHO, 2018), with prevalence rates between 13 and 27% in western countries like the US (van Cleave et al., 2010). Although there is no consensual definition of CC, these non-communicable diseases are typically characterized by a long duration (at least three months; van der Lee et al., 2007), functional impairment (van der Lee et al., 2007), absence of cure or presence of disease progression (Stanton et al., 2007), physical disability or pain (de Ridder et al., 2008), and the need for extensive (continuous) medical and psychological care (Mokkink et al., 2008).

Functional impairments in daily lives due to the CC are substantial, and include hampered school attendance, interference with positive relationships to peers or social isolation, as well as specific challenges associated with the medical therapy and adherence to treatment (Compas et al., 2012). Thus, CC interfere with normal psychosocial development and can lead to negative psychological outcomes in youth, like prolonged stress (Compas et al., 2012), reduced quality of life (QoL; Holmbeck et al., 2002) or symptoms of depression (Pinquart and Shen, 2011) and anxiety (Cobham et al., 2020). Although effective psychotherapeutic interventions for these mental health issues exist (Zhou et al., 2015; Zhou et al., 2019), the availability and uptake of evidence-based face-to-face treatments is limited (Gloff et al., 2015) due to different structural and individual barriers, involving shortage of service

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supplies with long waiting times (Andrade et al., 2014), high economic costs (Mojtabai, 2005), or stigma threat (Gulliver et al., 2010).

Digital health interventions, delivered via the Internet or mobile devices, might be a promising alternative to overcome these barriers and contribute to the extension of mental health care practices for children and adolescents with CC (Lunkenheimer et al., 2020). Possible advantages of Internet- and mobile-based interventions (IMIs) might be their delivery mode irrespective of the constraints of space and time, potential anonymity and flexibility in conduct, special attractiveness for youth, potential cost-effectiveness, as well as scalability on a larger scale on a steady basis (Andersson et al., 2019; Domhardt et al., 2018; Domhardt and Baumeister, 2018; Ebert et al., 2018). Obviously, some assets are especially important when the access to conventional mental health care services for youth with CC is even further reduced – as observed during the Covid-19 crisis (Torous and Wykes, 2020). Regardless of contemporary circumstances, IMIs can be implemented as stand-alone interventions, as part of blended-therapy approaches or within a framework of stepped and collaborative care (Andersson et al., 2019; Domhardt et al., 2018; Domhardt and Baumeister, 2018; Ebert et al., 2018; Yonek et al., 2020). Of note, interventions with accompanying human support evince consistently higher effect sizes than pure self-help interventions for depression and anxiety symptoms in adults (Baumeister et al., 2014; Domhardt et al., 2019), reaching even comparable effect sizes to face-to-face psychotherapies in some instances (Carlbring et al., 2018). Meta-analytic evidence also indicates that internet-based interventions are efficacious in treating symptoms of anxiety and depression in children and adolescents, with medium to large and small to medium effect sizes respectively (Domhardt et al., 2020b). There are also preliminary indications derived from single studies that internet-based interventions might be acceptable (Lenhard et al., 2017) and cost-effective in youth (Jolstedt et al., 2018).

However, the evidence-base in regard to the efficacy of IMIs specific for youth with CC and comorbid mental health problems is fragmented and constrained by several shortcomings. For example, Vigerland et al. (2016) found in subgroup analyses a medium overall effect (standardized mean difference, SMD, 0.85; 95% CI, 0.63 to 1.07) for internet-based cognitive behavior therapy (iCBT) for some somatic conditions (i.e., functional gastrointestinal disorder, insomnia and chronic pain), omitting mobile-based interventions and therapeutic approaches beyond CBT. Furthermore, Fedele et al. (2017) found a small effect for mobile-based interventions for various health outcomes in youth with or without CC (SMD, 0.22; 95% CI, 0.14 to 0.29), reporting only an overall estimate with high clinical heterogeneity and neglecting fine-grained analyses on specific outcomes and subgroups. Other meta-analyses were constrained by a small number of included trials (Low and Manias, 2019; Thabrew et al., 2018), focusing either on specific control conditions (i.e., treatment-as-usual; Low and Manias, 2019) or psychological outcomes (i.e., symptoms of depression and anxiety; Thabrew et al., 2018), evincing non-significant findings for QoL, self-efficacy, and self-management (Low and Manias, 2019), as well as depression and anxiety symptom severity (Thabrew et al., 2018). Altogether, important research questions in regard to the efficacy and effect-modifying factors of IMIs for youth with CC are unsettled to date.

Hence, this meta-analysis aims to extend the current evidence-base by comprehensively investigating the efficacy of IMIs for novel and (disorder-)specific outcomes, as well as by resolving methodological shortcomings of prior reviews, focusing on three overarching research questions: First, to assess the efficacy of IMIs in improving psychological outcomes (i.e., depression, anxiety and stress symptom severity, as well as QoL and self-efficacy) in youth with CC. Second, to assess the efficacy of IMIs in improving disease-related physical/somatic outcomes, self-management and treatment adherence in regard to the CC. Third, to identify moderators of intervention effects.

2. Method

This meta-analysis is reported in accordance to the PRISMA guidelines (Moher et al., 2009; Table S1 in the supplementary material) and was registered with Open Science Framework (https://osf.io/83cwt/).

2.1. Eligibility criteria

Only randomized controlled trials (RCTs) published in English language were eligible for inclusion. Participants were children and adolescents (0–18 years; mean age $\leq$ 18) diagnosed with a CC, with the diagnosis established by a qualified health care professional or confirmed by valid diagnostic instruments. All CC as defined by the WHO (2018) and van der Lee et al. (2007) were eligible for inclusion. Interventions had to be delivered digitally via Internet- or mobile-based communication technology (e.g., web-platform, mobile health app for smartphones or tablets) and had a psychotherapeutic or medical focus (i.e., provided health- and/or mental-health-related support, with or without human guidance in an individual setting; group-based interventions were not included). Comparison conditions eligible for inclusion were various active and passive control groups (e.g., wait-list, treatment-as-usual or active treatments). Outcomes were mental health symptoms, physical/somatic symptoms related to the CC, QoL, self-efficacy, self-management and treatment adherence in regard to the CC. Outcome measures eligible for inclusion were standardized questionnaires or structured interviews, relying on self-, and/or parent report, or clinician ratings. Studies that evaluated IMIs targeting parents or legal guardians of youth with CC were also included, as long as they were primarily intended to improve outcomes in children ($\leq$12 years) and adolescents (13–18 years).

2.2. Literature search and study selection

The search strategy was twofold. First, systematic searches were conducted in CENTRAL, Embase, MEDLINE/PubMed and PsycINFO, with a predefined set of search strings specifically developed for each database in Ovid, from database inception to May 15, 2019 (Table S2 in the supplementary material/e-Component). Second, reference lists of all eligible studies and other relevant reviews (Fedele et al., 2017; Kew and Cates, 2016; Lancaster et al., 2018; Thabrew et al., 2018) were manually searched to identify further studies that met our inclusion criteria.

One reviewer (A.S.) screened all titles and abstracts and discarded obviously irrelevant articles. Afterwards, the full texts of all potentially relevant articles were screened in terms of the aforementioned eligibility criteria independently by two reviewers (A.S. and L.S.).

2.3. Data extraction

Two independent reviewers (A.S. and L.S.) extracted data from the included studies. Disagreements were solved by consultation of a third reviewer (M.D.).

2.4. Risk of bias assessment

The methodological quality of included studies was assessed independently by two reviewers (A.S. and L.S.) with the Cochrane risk of bias assessment tool (Higgins et al., 2011) on all seven criteria: (1) random sequence generation, (2) allocation concealment, (3) blinding of participants and personnel, (4) blinding of outcome assessment, (5) incomplete outcome data, (6) selective reporting and (7) other bias. Of note, although blinding of participants and personnel is hardly to be achieved in psychotherapy research (Munder and Barth, 2018), it might be principally possible in pure self-help IMIs (Domhardt et al., 2020a; Furukawa et al., 2019).

The included studies were rated as having “low”, “unclear” or “high risk of bias” on each domain. Inter-rater reliability was calculated using

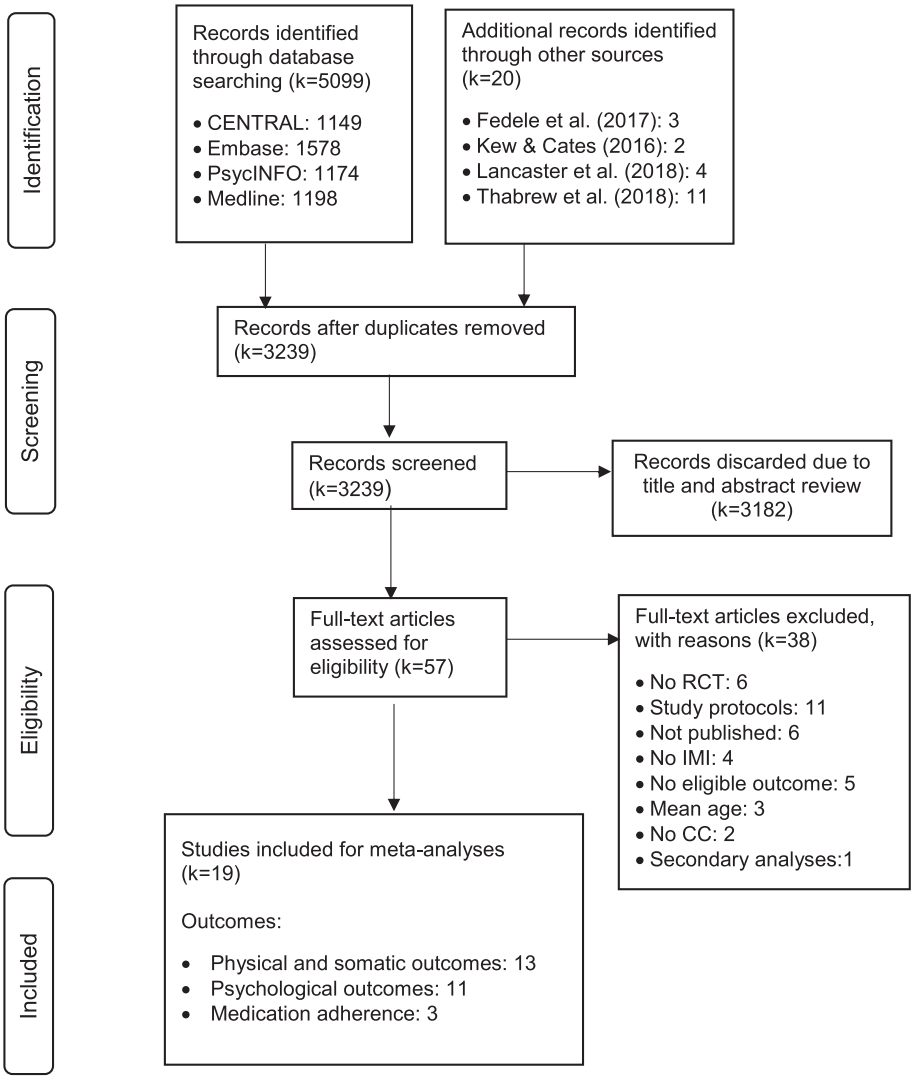


Fig. 1. PRISMA flow chart.

Cohen's Kappa.

2.5. Data analysis

Random effects meta-analyses were performed to compute estimates of intervention effects for each a priori defined primary and secondary outcomes, contrasted with either active, passive or combined (i.e., active and passive) control conditions. Standardized mean differences (SMD) with 95% confidence intervals (95% CI) were calculated for continuous outcomes. Hedges' *g*, which corrects for biases due to small sample sizes (Cuijpers, 2016), was deployed.

Statistical heterogeneity was assessed with Cochran's *Q* and the I^2-statistic, which designates the level of heterogeneity in percentages (Cuijpers, 2016; Higgins et al., 2003). It is assumed that a percentage of 25% indicates low, 50% moderate and 75% high statistical heterogeneity (Higgins et al., 2003). Forest plots were used for a visual presentation of the presence and nature of statistical heterogeneity. The possible influence of publication bias was planned to be determined by Egger's regression test for funnel plot asymmetry (at least 10 trials per meta-analysis; Higgins and Green, 2011) and the trim-and-fill method (Duval and Tweedie, 2000).

In order to identify possible moderators, subgroup analyses were intended to be performed in case of three or more studies per subgroup for: (1) variations of IMIs (internet-based psychotherapy, guided self-help, unguided self-help), (2) type of delivery (internet- vs. mobile-based), (3) psychotherapeutic background (CBT vs. other approaches), (4) type of CC, (5) participants (children, adolescents, parents/caregivers or families), (6) type of outcome assessment (self-report or ratings by parents/caregivers or clinicians/personnel), (7) type of control condition and (8) study quality.

3. Results

3.1. Study selection

The systematic literature search identified a total of 5099 references. Finally, 19 studies (Berndt et al., 2014; Carlsen et al., 2017; Fiks et al., 2015; Franklin et al., 2006; Guendelman et al., 2002; Gustafson et al., 2012; Hanberger et al., 2013; Hicks et al., 2006; Jan et al., 2007; Johnson et al., 2016; Joseph et al., 2013; Law et al., 2015; Newcombe et al., 2012; Newton et al., 2009; Newton and Ashley, 2013; Nijhof et al., 2012; Palermo et al., 2009; Stinson et al., 2010; Stinson et al., 2016) representing 2410 participants fulfilled our eligibility criteria and were included in this meta-analysis. The detailed study selection process and reasons for exclusion are outlined in the PRISMA flow chart in Fig. 1.

Table 1
Main characteristics of included studies.

Study	Chronic condition	Population (recruitment)	Age M (SD); range	Intervention (name)	Theoretical foundation/ treatment approach	Intervention components	Control group	Primary outcome	Post-treatment (weeks)	Follow-up (months)
Berndt et al. (2014)/GER	Type-1 diabetes	68 children and adolescents (clinic)	13.05 (2.45); 8–18	TAU plus mobile or web-based disease monitoring applications (*Mobil Diab*)	German Diabetes Association guidelines	Telemonitoring: tracks health information, sharable with professionals and family members	TAU	Anthropometric data; metabolic control parameters; diabetes-related knowledge/ children and adolescents	4	–
Carlsen et al. (2017)/ DNK	Inflammatory bowel disease	29 children and adolescents (clinic)	14.86 (–); 10–17	Web-based disease monitoring	Patient-managed eHealth, with symptom-monitoring; Constant -care.com	Symptom monitoring with electronic traffic light system: schedules next treatment depending on cut off scores	TAU	Ability of the program (Individual treatment intervals)/children and adolescents	4–12	24 (max.)
Fiks et al. (2015)/USA	Asthma	60 parents (clinic)	8.3 (1.9); 6–12	Web-based support portal (*MyAsthma*)	Decision support system to both clinicians and parents; electronic health records	Identification of parents' concerns and goals for asthma treatment; tracking of symptoms, medication side effects & progress toward goals; asthma educational content; access to the asthma care plan	TAU plus decision support system	Acceptability of asthma care/ parents and clinicians; satisfaction with the portal, experience using the portal/ parents and clinicians	26	–
Franklin et al. (2006)/UK	Type-1 diabetes	92 children and adolescents (clinic)	13.17 (–);8–18	TAU plus mobile-based support system (*Sweet Talk*)	Social cognitive theory	Automated, scheduled text messaging system: weekly reminder of goals set, daily tips to reinforce & optimize self-management and control	TAU	Glycemic control (HbA1c); Self-efficacy (SED)/children and adolescents; Diabetes knowledge (DKN)/children and adolescents; Social support (DSSI)/children and adolescents	52	–
Guendelman et al. (2002)/USA	Asthma	134 children and adolescents (clinic)	12.1 (2.6); 8–16	Web-based self-management education program (*Health Buddy*)	The National Heart, Lung and Blood Institute recommendations	Interactive communication device: instant feedback about asthma symptoms, use of medication and health service, school attendance and activities	Asthma diary	Physical activity	6	3
Gustafson et al. (2012)/USA	Asthma	301 families (managed care organizations)	7.92 (2.52); 4–12	Mobile-based support system (*CHESS*) plus case management	Self-efficacy theory	Psychoeducation, adherence strategies, decision-making tools, and support services; monthly calls to the parent; medication adherence; symptom-monitoring; psychosocial challenges and support	TAU plus asthma information	Symptom free days; adherence to Asthma controller medications (diary)/children	12	6,9,12
Hanberger et al. (2013)/SWE	Type 1 diabetes	474 families (clinic)	13.25 (3.7); 0–18	Web-based network and education portal (*Diabit*)	Self-management; user-centred design process; web 2.0 portal	Self-management portal: diabetes-related information, social networking functions, enabling communication with peers and health-professionals; services for medical prescription renewal, appointments, etc.	TAU	Clinical variables (HbA1c, numbers of severe hypoglycemia)	52	–
Hicks et al. (2006)/CAN	Pediatric Pain	47 families (physicians' offices and school)	11.7 (2.1); 9–16	Web-based CBT program	CBT	Relaxation techniques, cognitive strategies, psychoeducation, positive lifestyle choices (e.g. on diet, exercise, and social activity)	Wait-list	Pain (diary)/children and adolescents	11	5
Jan et al. (2007)/ TWN	Asthma	164 children (clinic)	10.44 (2.83); 6–12	Web-based educational and monitoring program (*Blue Angel*)	Global Initiative for Asthma program guidelines	Internet-based diary cards for symptom recording, peak expiratory flow rate, symptomatic support information; action plan; uploading and retrieving data for personal and physicians use	TAU plus asthma diary	PEF records/children; Asthma symptom (diary)/children; Pulmonary spirometric tests; Pediatric Asthma Quality of Life/children and caregivers; Childhood ACT/children and	12	–

(*continued on next page*)

Table 1 (*continued*)

Study	Chronic condition	Population (recruitment)	Age M (SD); range	Intervention (name)	Theoretical foundation/ treatment approach	Intervention components	Control group	Primary outcome	Post-treatment (weeks)	Follow-up (months)
								caregivers; Survey of asthma knowledge/caregivers; Treatment adherence (ACT)/ children; Adherence to the diaries (survey on satisfaction)/ children		
Johnson et al. (2016)/USA	Asthma	98 adolescents (academic medical center)	14.05 (1.68); 12–17	Web-based application medication monitoring and SMS dosing reminders (*MMH*)	Behavior change theory	Tools to create and print a structured medication list, to attach a dosing schedule to each medication, to request a text-message reminder for each dose, and to visualize medication adherence performance for each medication	TAU and action list	Asthma management self-efficacy (Child Asthma Self-Efficacy Scale)/adolescents	3	–
Joseph et al. (2013)/USA	Asthma	422 adolescents (school)	15.6 (–); 15–19	Web-based, tailored intervention (*Puff City*)	Health belief model, attribution theory, behavioral theory, motivational interviewing	Health messages and information on medication adherence, "inhaler nearby", smoking reduction/ cessation; tailored feedback; risk assessment reports; four submodules on (e.g., emotional support, motivation, etc.)	Generic asthma education	–	52	–
Law et al. (2015)/USA	Pediatric Headache	83 families (clinic)	14.5 (1.7); 11–17	Web-based family CBT (*Web-MAP*) plus specialized headache treatment	CBT	Education; relaxation; cognitive strategies; sleep hygiene education; operant training; communication	Specialized head-ache treatment	Headache frequency (diary)/ adolescents	8–10	3
Newcombe et al. (2012)/AUS	Chronic respiratory condition	42 children and adolescents (clinic)	13.58 (1.92); 10–17	Web-based problem-solving program (*Breathe Easier Online*)	Problem solving therapy	Interactive online skills training that targeted problems in general in addition to illness-specific problems; (a)synchronous communication platform for peers; homework assignments	Wait-list	Depression (CES-DC)/children and adolescents; Social problem solving (SPSI-R:SF)/children and adolescents	9	–
Newton et al. (2009)/NZL	Type 1 diabetes	78 adolescents (diabetes services)	14.4 (2.37); 11–18	Pedometer plus Mobile-based weekly text messages	American Diabetes Association recommendations	Pedometers and motivational text messages to increase physical activity	TAU	Physical activity (step count and self-report)/adolescents	12	–
Newton and Ashley (2013)/USA	Type-1 diabetes	59 adolescents (Diabetes Center)	14.5 (–); 13–18	Web-based networking portal (*Diabetes Teen Talk*)	Bandura's self-efficacy theory	Blog, chat room and discussion forums with weekly topics ("Frustrations with diabetes"; "Benefits of good control"; "Family"; "Friends"; "Body image, exercise and diet"; "Community, school and sports"; "Worries about diabetes")	TAU	HRQOL (DQOLY)/adolescents; Self-Efficacy (Diabetes Self-Management)/adolescents; Outcome Expectations (Diabetes Self-Management)/ adolescents	7	–
Nijhof et al. (2012)/NLD	Chronic fatigue syndrome	135 adolescents (clinic)	15.85 (1.3); 12–18	Web-based CBT (*FITNET*)	CBT	Guided and tailored iCBT with 21 modules and a comprehensive psychoeducation part (e.g., goals; sleep routine; cognition; fatigue specific interventions; physical activities and balance)	TAU	School attendance (percentage of the normal school schedule)/ parents; Fatigue (CIS-20)/ adolescents; Physical functioning (CHQ-CF87)/ adolescents	26	–
Palermo et al. (2009)/USA	Pediatric Pain	48 families (clinic)	14.8 (2.0); 11–17	Web-based family CBT (*Web-MAP*)	CBT and social learning frameworks	Child modules (psychoeducation; stress & negative emotions; deep breathing & relaxation;	Wait-list	Activity limitations (CALI)/ children and adolescents; Pain	8–10	3

(*continued on next page*)

Table 1 (*continued*)

Study	Chronic condition	Population (recruitment)	Age M (SD); range	Intervention (name)	Theoretical foundation/ treatment approach	Intervention components	Control group	Primary outcome	Post-treatment (weeks)	Follow-up (months)
						distraction; cognitive skills; sleep hygiene and lifestyle; staying active; relapse prevention) Parent modules (psychoeducation; stress & negative emotions; operant strategies; modeling; sleep hygiene & lifestyle; communication; relapse prevention)		(diary)/children and adolescents		
Stinson et al. (2010)/CAN	Juvenile idiopathic arthritis	46 adolescents (care center)	14.5 (1.48); 12–18	Web-based self-management program (*Teens Taking Charge*) plus telephone support	Multicomponent treatment protocol based on self-management strategies, disease-specific information, and social support	Arthritis-specific information/ psychoeducation; arthritis medications; managing symptoms, stress and negative thoughts; relaxation; distraction; other types of care (exercise, nutrition, splints); self-monitoring and supports; lifestyle issues; transitional care issues; two modules specifically for parents/ caregivers	Tele-phone support	HRQOL (JAQQ)/adolescents and parents	12	–
Stinson et al. (2016)/CAN	Juvenile idiopathic arthritis	30 adolescents (clinic)	14.3 (1.7); 12–18	Web-based mentoring program (*iPeer2Peer*)	Peer mentoring with a focus on skills training, self-management and social support strategies	Peer mentoring program with 10 sessions of 20–30 min Skype video calls; the training manual for peers provided suggested topics (e.g., coping strategies, lifestyle management, communication)	Wait-list	Feasibility (recruitment and withdrawal rates, program adherence, completed questionnaires, program engagement and satisfaction)/ adolescents	8	–

Abbreviations: ACQ, Asthma Control Questionnaire; ACT, asthma control test; ARCS, Adult Responses to Children's Symptoms; AUS, Australia; BMI, body mass index; CDI, Children's Depression Inventory; CALI, Child Activity Limitations Interview; CAN, Canada; CASES, Children's arthritis self-efficacy; CBT, cognitive behavior therapy; CES-DC, Center for Epidemiologic Studies Depression Scale for Children; CHQ-CF87, child health questionnaire physical functioning subscale; CIS, checklist individual strength; DISABKIDS, Quality of live questionnaires for children with chronic conditions; DKA, diabetic ketoacidosis; DKN, diabetes knowledge score; DNK, Denmark; DQOLY, quality of life for youth scale; DSSI, diabetes social support interview; ED, emergency department; GER, Germany; HRQOL, health related quality of life; IFX, infliximab; JAQQ, Juvenile Arthritis Quality of Life Questionnaire; M, mean; Max, maximal; MEPS, Medical issues, exercise, pain and social support questionnaire; MMH, MyMediHealth; NA, not applicable; NLD, Netherlands; NLZ, New Zealand; PAQLQ, Pediatric Asthma Quality of Life Questionnaire; PedsQL, Pediatric Quality of Life Inventory; PEF, peak expiratory flows; PSQ, perceived severity of stress questionnaire; QPP, Patients' Perspective questionnaire; RCADS, Revised Child Anxiety and Depression Scale; RCMAS, Revised Children's Manifest Anxiety Scale; RPI, Recalled Pain Inventory; SD, standard deviation; SED, self-efficacy for diabetes; SPSI-R:SF, Social Problem-Solving Inventory–Revised Short Form; SQOL, subjective quality of life; SWE, Sweden; SWE-DES-SF, Swedish Diabetes Empowerment Scale, short version; TAU, Treatment as usual; TWN, Taiwan; UK, United Kingdom, VAS, visual analogue scale.

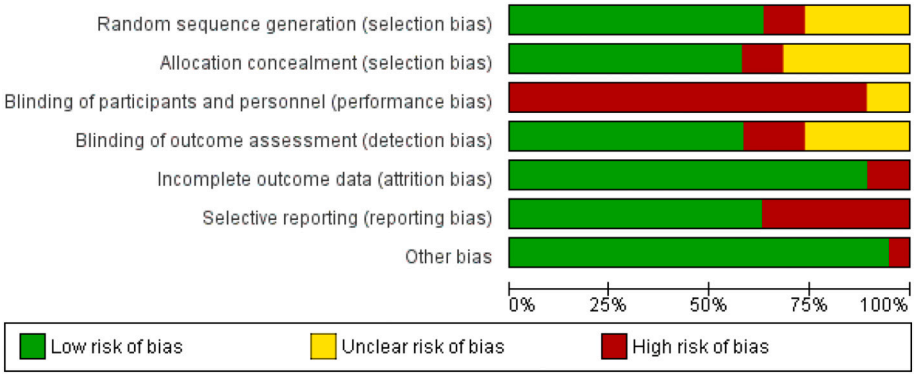


Fig. 2. Risk of bias assessment presented as percentages across all included studies.

3.2. Study characteristics

The main characteristics of included studies are detailed in Table 1. Of the 19 eligible RCTs, five studies focused on diabetes (Franklin et al., 2006; Newton et al., 2009; Hanberger et al., 2013; Newton and Ashley, 2013; Berndt et al., 2014), seven on chronic respiratory conditions – among them six exclusively on asthma – (Fiks et al., 2015; Guendelman et al., 2002; Gustafson et al., 2012; Jan et al., 2007; Johnson et al., 2016; Joseph et al., 2013; Newcombe et al., 2012), three on pediatric pain (Hicks et al., 2006; Law et al., 2015; Palermo et al., 2009), two on juvenile idiopathic arthritis (Stinson et al., 2010; Stinson et al., 2016), and one study each on chronic fatigue syndrome (Nijhof et al., 2012) or inflammatory bowel disease (Carlsen et al., 2017). The vast majority of studies (94.7%) were conducted in western countries. Seven trials enrolled adolescents, five mixed samples of children and adolescents, five used families as entity for analysis and one trial either only children or parents. The mean sample size was 127 patients (SD = 129.88), with a mean age of 13.2 years (SD = 2.23), and 60.6% of participants were being females. Internet-based interventions were evaluated in 13 studies (68.4%) and mobile-based interventions were examined in three studies (15.8%); interventions combining web-based and mobile-based components were evaluated in three studies (15.8%). The three most frequently researched theoretical foundations and treatment approaches in IMIs were CBT (k = 4 studies; 21.0%), disorder-specific treatment guidelines (k = 4; 21.0%) and self-efficacy or self-management approaches (k = 4; 21.0%). Other theoretical orientations and treatment approaches evaluated in one study each (k = 1; 5.3%) were problem-solving therapy, skills-training, social cognitive theory, symptom-monitoring, decision-support-systems, behavior change and mixed approaches. Post-treatment assessment was 17 weeks (SD = 16.52) after base-line on average.

3.3. Risk of bias assessment

The results of the risk of bias assessments are detailed in Figs. 2 and 3. The criterion least met was blinding of participants/personnel, as most studies were rated with a high risk of bias on this domain (89%). In the other domains, studies were predominantly rated with low risk of bias (random sequence generation: 63%; allocation concealment: 58%; blinding of outcome assessment: 58%; incomplete outcome data: 89%; selective reporting: 63%; other bias: 95%). The inter-rater reliability between reviewers was adequate (Cohen's Kappa = 0.78).

3.4. Meta-analyses

Random-effects meta-analyses were performed on 16 comparisons altogether (Table 2). Studies that reported multiple outcome measures for the same outcome domain were aggregated into a single effect size for each outcome.

An overall effect size was calculated for all psychological and disease-related outcomes combined, resulting in a non-significant Hedges` g of −0.08 (95% CI, −0.17 to 0.00; k = 19 studies; n = 2410 participants; I^2 = 0%; Fig. S1).

3.5. Primary outcomes

One effect size was calculated for all psychological outcomes (studies that reported multiple outcomes were aggregated into a single effect size). IMIs showed no significant improvement in psychological outcomes at post-intervention when compared to controls (g = −0.14; 95% CI, −0.30 to 0.02; k = 11; n = 598; I^2 = 0%; Fig. S2).

3.5.1. Depression symptom severity

For depression severity at post-intervention, IMIs evinced no significant differences compared to control conditions (g = −0.29; 95% CI, −0.63 to 0.05; k = 3; n = 134; I^2 = 0%; Fig. S3).

3.5.2. Quality of life

IMIs showed no significant differences in the level of QoL at post-intervention compared to controls (g = −0.04; 95% CI, −0.24 to 0.15; k = 7; n = 403; I^2 = 0%; Fig. S4).

3.5.3. Self-efficacy

A small effect was found in favor of IMIs compared to non-active control conditions for increasing the level of self-efficacy at post-intervention (g = 0.38; 95% CI, 0.15 to 0.61; k = 5; n = 300; I^2 = 0%; Fig. S5).

3.6. Secondary outcomes

One effect size was calculated for all disease-related physical and somatic outcomes combined (multiple outcomes were aggregated into a single effect size). IMIs revealed a small significant effect in improving disease-related somatic outcomes at post-intervention compared to controls (g = −0.13; 95% CI, −0.25 to −0.01; k = 13; n = 1676; I^2 = 21%; Fig. S6).

3.6.1. Diabetes related outcome

The aggregated effect size for changes in HbA1c in comparison of IMIs to non-active controls at post-intervention was not significant (g = −0.03; 95% CI, −0.18 to 0.12; k = 4; n = 680; I^2 = 0%; Fig. S7).

3.6.2. Chronic respiratory diseases related outcomes

The efficacy for asthma symptoms was evaluated with random-effects meta-analyses specific for day and night symptoms. IMIs evinced no significant differences on day (g = −0.13; 95% CI, −0.35 to 0.09; k = 3; n = 628; I^2 = 34%; Fig. S8) and night symptom severity (g = −0.05; 95% CI, −0.2 to 0.11; k = 3; n = 628; I^2 = 0%; Fig. S9) at post-

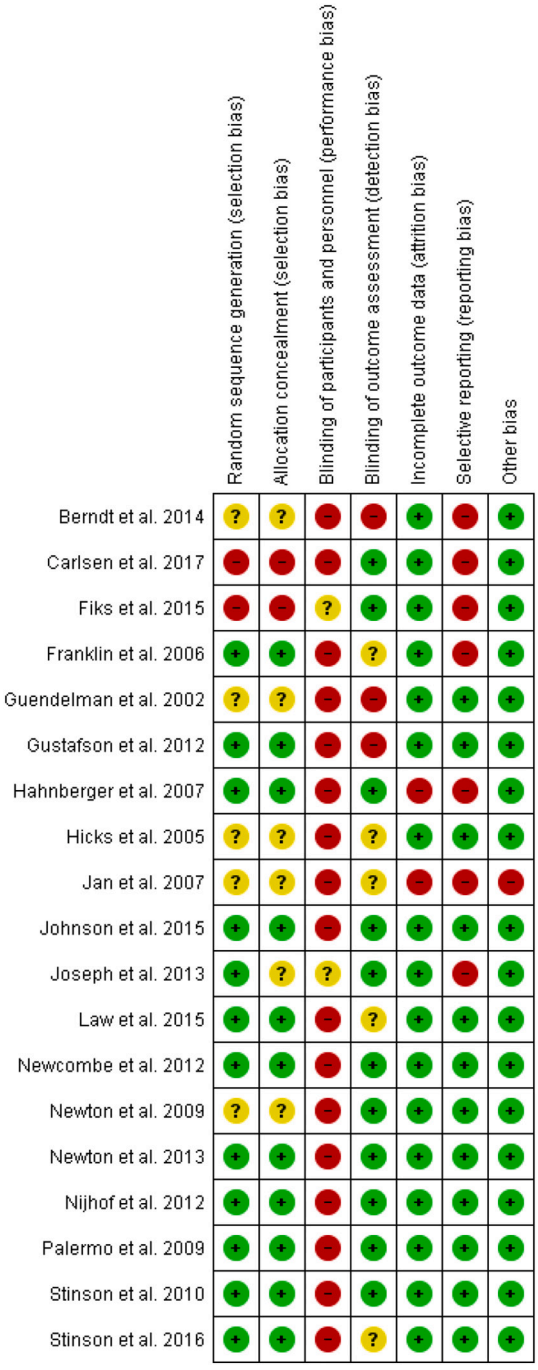


Fig. 3. Risk of bias assessment: review authors' judgements about each risk of bias item for each included study.

intervention when compared to active controls. Furthermore, the effect size on the number of missed school days in patients with asthma revealed no significant differences ($g = -0.11$; 95% CI, −0.29 to 0.07; k = 2; $n = 475$; $I^2 = 0\%$; Fig. S10).

3.6.3. Health service utilization

The two meta-analyses on the number of care visits revealed no advantages of IMIs, either when they were compared to combined control conditions ($g = -0.02$; 95% CI, −0.17 to 0.13; k = 4; $n = 663$; $I^2 = 0$; Fig. S11) or compared to active controls only ($g = -0.05$; 95% CI, −0.21 to 0.11; k = 3; $n = 603$; $I^2 = 0$; Fig. S12). Furthermore, no significant differences in the number of hospitalizations at post-intervention were found between IMIs and active controls ($g = -0.38$; 95% CI, −0.85 to 0.1; k = 3; n = 603; $I^2 = 82\%$; Fig. S13).

3.6.4. Pain intensity

The meta-analysis for pain intensity at post-intervention missed statistical significance, favoring IMIs compared to combined controls conditions ($g = -0.33$; 95% CI, −0.67 to 0.02; k = 5; $n = 240$; $I^2 = 43\%$; Fig. S14). When excluding the single study with an active comparison condition (Law et al., 2015), the meta-analysis revealed a moderate effect size in favor of IMIs compared to non-active controls in reducing pain intensity ($g = -0.5$; 95% CI, −0.81 to −0.18; k = 4; $n = 163$; Fig. S15), with reduced statistical heterogeneity ($I^2 = 0\%$).

3.6.5. Medication adherence

No significant differences were found for medication adherence at post-intervention between IMIs and active controls ($g = -0.15$; 95% CI, −0.58 to 0.28; k = 3; $n = 412$; $I^2 = 68\%$; Fig. S16).

3.7. Subgroup analyses and assessment of publication bias

Subgroup analyses were not possible, because of the limited number of trials per subgroup except for analyses on QoL. The analyses for studies focusing on type-1 diabetes (Berndt et al., 2014; Newton et al., 2009; Newton and Ashley, 2013) and studies investigating diseases other than diabetes (Hicks et al., 2006; Johnson et al., 2016; Stinson et al., 2010; Stinson et al., 2016) did not result in significant differences in the level of QoL at post-intervention (Fig. S17). Pre-planned analyses to determine the possibility of publication bias were not feasible, because of the small number of studies per comparison.

4. Discussion

This systematic review comprehensively evaluated research investigating the efficacy of digital health interventions in improving psychological and disease-related outcomes in youth with CC. Altogether, 19 RCTs representing 2410 patients were identified and included in this meta-analysis. Our results indicate that IMIs might be beneficial in improving levels of self-efficacy and some disease-related somatic outcomes; however, the effect sizes were small (to moderate) and most meta-analytic comparisons revealed no beneficial effects of IMIs over control conditions on a range of outcomes. These findings are in line with previous reviews (Kew and Cates, 2016; Lancaster et al., 2018; Thabrew et al., 2018), suggesting a limited benefit of IMIs in children and adolescents with CC. This empirical knowledge is of high relevance, since the digitalization of psychotherapeutic and psychosocial interventions is often considered as a powerful way – or even panacea – to overcome existing treatment gaps. Yet, the present study points to the need to look carefully on the specific benefits and limitations of IMIs in different populations and health care settings, especially when it comes to pediatric patients with comorbid mental health symptoms.

The ability to cope and psychologically adjust to CC is of great importance (de Ridder et al., 2008), and patients` self-efficacy beliefs (Bandura, 1978) and self-management (Ng et al., 2018) might be key to this endeavor. We found evidence that IMIs can increase the levels of self-efficacy in regard to the disease in children and adolescents with CC; a finding which is consistent with research by Lancaster et al. (2018) that has documented an increase in self-efficacy in patients through digital monitoring tools too. In their review of 13 RCTs, they also found promise that IMIs might increase the disease-related self-management in youth, which was not corroborated in our meta-analysis. Principally, the strength of IMIs to support the self-efficacy and self-management in juvenile patients seems not to be comparable to the magnitude of IMIs in adults with CC, consistently evincing larger effect sizes for a range of psychological outcomes (Bendig et al., 2018).

Furthermore, except for the meta-analyses on disease-related somatic outcomes and pain intensity (compared to non-active controls), our meta-analytic review revealed predominantly non-significant

Table 2
Meta-analytic comparisons.

Outcome	k	Controls	Sample size (IG/CG)	Meta-analyses			Heterogeneity		
				g	P	95% CI	Q	P	I^2 (%)
Primary outcomes									
All psychological outcomes	11	Any control condition	308/290	−0.14	0.09	−0.30, 0.02	8.49	0.58	0
Depression symptom severity	3	Any control condition	69/65	−0.29	0.1	−0.63, 0.05	1.96	0.37	0
QoL	7	Any control condition	205/198	−0.04	0.67	−0.24, 0.15	2.4	0.88	0
Self-efficacy	5	Non-active control condition	156/143	0.38	0.001	0.15, 0.61	2.44	0.65	0
Secondary outcomes									
All somatic outcomes	13	Any control condition	851/825	−0.13	0.03	−0.25, −0.01	15.27	0.23	21
Type-1 diabetes									
HbA1c	4	Non-active control condition	349/331	−0.03	0.67	−0.18, 0.12	1.87	0.6	0
Asthma									
Day symptoms	3	Active control condition	312/316	−0.13	0.25	−0.35, 0.09	3.01	0.22	34
Night symptoms	3	Active control condition	312/316	−0.05	0.56	−0.20, 0.11	0.58	0.75	0
Missed school days	2	Active control condition	230/245	−0.11	0.24	−0.29, 0.07	0	0.99	0
Health care utilization									
Care visits	4	Any control condition	326/337	−0.02	0.8	−0.17, 0.13	2.52	0.47	0
Care visits	3	Active control condition	293/310	−0.05	0.54	−0.21, 0.11	0.98	0.61	0
Hospitalization	3	Active control condition	293/310	−0.38	0.69	−0.85, 0.1	16.42	<0.001	82
Pain									
Pain intensity	5	Any control condition	127/113	−0.33	0.06	−0.67, 0.02	6.94	0.14	43
Pain intensity	4	Non-active control condition	87/76	−0.5	0.002	−0.81, 0.18	1.95	0.58	0
Adherence									
Medication adherence	3	Active control condition	206/206	−0.15	0.5	−0.58, 0.28	6.22	0.04	68

Abbreviations: CG, control group; IG, intervention group; IMI, internet- and mobile-based intervention; k = number of studies; QoL, quality of life.

findings. These rather sobering results are in accordance with prior reviews (Kew and Cates, 2016; Lancaster et al., 2018; Thabrew et al., 2018), which equally could not find beneficial effects of IMIs in youth with CC for a range of psychological and disease-related outcomes, like depression and anxiety symptoms (Thabrew et al., 2018), QoL (Lancaster et al., 2018), disease status (Kew and Cates, 2016; Thabrew et al., 2018), health service utilization (Kew and Cates, 2016; Lancaster et al., 2018), and medication adherence (Lancaster et al., 2018). However, since we were able to include substantially more studies than former meta-analyses and evaluated novel outcomes additionally, the current findings are more robust and further underpin the assumption that IMIs might not be as powerful in pediatric patients with CC than in youth with mental disorders alone (Domhardt et al., 2020b; Vigerland et al., 2016) or in youth without clinically relevant pathology (Fedele et al., 2017). Nevertheless, since some comparisons only scantly missed significance, other reviews have revealed more encouraging findings for IMIs (Fedele et al., 2017; Hieftje et al., 2013), the question arises why the findings of the current meta-analysis are rather disenchanting. This is even more pressing, since the evidence-base for the effectiveness for psychological treatments delivered face-to-face for various mental health issues for youth without CC is well-ascertained (Zhou et al., 2015; Zhou et al., 2019), and there is some evidence that these interventions are also effective for several outcomes in youth with CC (Bennett et al., 2015; Kahana et al., 2008; Kibby et al., 1998; Sanders et al., 1994). For example, two systematic reviews revealed that face-to-face psychological interventions are effective for disease-management and emotional/behavioral problems (Kibby et al., 1998), as well as for symptoms of depression and anxiety (Bennett et al., 2015) in children and adolescents with CC, all with large effect sizes respectively. Similar to the theoretical foundations of IMIs found in our study, the majority of interventions in both reviews (Bennett et al., 2015; Kibby et al., 1998) were based on principles of CBT and related behavioral interventions.

The present predominantly non-significant findings in our meta-analysis might be due to several reasons. First, some IMIs had no clear psychotherapeutic foundation and were merely intended to assist the patients` self-management in one specific aspect (e.g., monitoring) and not to reduce mental health symptoms – while these outcomes were assessed in primary studies. As such, some interventions themselves might not have been suitably designed in order to achieve relevant effect sizes for youth with CC, lacking sophisticated psychotherapeutic components and strategies directly targeting comorbid mental health symptoms. Furthermore, a substantial number of IMIs (8 out of 19) are older than ten years, presumably not representative to the mobile technology and platforms available today. Second, although we were able to include substantially more studies than prior reviews (Low and Manias, 2019; Thabrew et al., 2018), single meta-analytic comparisons might be still underpowered to detect significant effects (Cuijpers et al., 2014; Harrer et al., 2019; Hedges and Pigott, 2001) – which might be in addition (very) small for single-component interventions, but clinically relevant for patients nonetheless (Domhardt et al., 2019). Third (and clinically most relevant), given the high strain and specific needs of youth with CC, it might be that this particular group of patients is not responsive to IMIs to the same extent than other patient populations (Andersson et al., 2019; Bendig et al., 2018; Domhardt et al., 2020b). Additionally, empirical knowledge on moderators, for example in regard to therapist involvement (Baumeister et al., 2014; Domhardt et al., 2020a; Reyes-Portillo et al., 2014), support by parents (Domhardt et al., 2020b; Fedele et al., 2017) or developmentally-related differences in age groups (Reins et al., 2020; Thabrew et al., 2018), is still largely pending, but is central to inform the allocation of individual patients to the most fitting psychological intervention, either delivered face-to-face or via digital technology. Next to these efforts toward precision medicine (Cohen and DeRubeis, 2018) and "*precision digital health*" (Domhardt et al., accepted), important future directions for forthcoming research are on how to best improve interventions and maximize treatment outcomes. At that, involving the patients` perspective into intervention development (Geirhos et al., submitted; Holmes et al., 2018; Low and Manias, 2019) and disentangling the active ingredients of interventions by means of component and mediation studies (Domhardt et al., 2020c) might be key avenues, to increase the potential benefits of digital health interventions for youth with CC and other underserved populations.

Besides several strengths (e.g., comprehensive scope, rigorous study selection and data extraction, low statistical heterogeneity across most meta-analyses and high overall quality of included studies), this review

has also limitations. First, the results need to be interpreted with caution, as the number of eligible studies was rather small and some pre-planned analyses on specific outcomes were not possible. Second, distinctive conclusions are challenging, because of differences in interventions and treatment approaches (Table 1), as well as types of CC diseases and outcomes. Third, the generalizability of this meta-analytic review might be curtailed, since the vast majority of studies were conducted in western countries and resorted to predominantly older female adolescents. Hence, generalizations should only be applied to the CC and populations included in this meta-analysis. Lastly, the intended tests for publication bias, as well as pre-planned subgroup and moderator analyses were not feasible, given the lack of maturity of this specific research field.

5. Conclusion

The findings of this meta-analysis point to a limited benefit and efficacy of digital health interventions in children and adolescents with CC. Yet, we also found indications that IMIs improve self-efficacy and disease-related somatic outcomes in pediatric patients, warranting further investigations. Moreover, future high-quality research is urgently needed, to identify factors contributing to improved user-centered interventions with better treatment outcomes; as well as to comprehensively weigh the actual potential of IMIs to (cost-)effectively scale up and complement collaborative mental health care for youth with CC.

Role of the funder

The funding source BMBF had no role in the study design, collection, analysis or interpretation of the data, writing the manuscript, or the decision to submit this paper for publication.

CRediT authorship contribution statement

Matthias Domhardt had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design: Domhardt, Schröder, Baumeister.

Acquisition, analysis, or interpretation of data: All authors.

Drafting of the manuscript: Domhardt, Schröder.

Critical revision of the manuscript for important intellectual content: All authors.

Statistical analysis: Schröder, Domhardt.

Administrative, technical, or material support: Baumeister, Schröder, Domhardt.

Supervision: Baumeister, Domhardt.

Declaration of competing interest

Harald Baumeister is a consultant for different insurance companies, health care associations, and psychotherapy chambers and gives talks and workshops and conducts third party-funded projects on e-health interventions. All authors declare that they have no conflicts of interest.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.invent.2021.100373.

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Chapter 4

Mobile-based interventions for common mental disorders in youth: A systematic evaluation of pediatric health apps

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Mobile-based interventions for common mental disorders in youth: a systematic evaluation of pediatric health apps

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Abstract

Background: The access to empirically-supported treatments for common mental disorders in children and adolescents is often limited. Mental health apps might extend service supplies, as they are deemed to be cost-efficient, scalable and appealing for youth. However, little is known about the quality of available apps. Therefore, we aimed to systematically evaluate current mobile-based interventions for pediatric anxiety, depression and posttraumatic stress disorder (PTSD).

Methods: Systematic searches were conducted in *Google Play Store* and *Apple App Store* to identify relevant apps. To be eligible for inclusion, apps needed to be: (1) designed to target either anxiety, depression or PTSD in youth (0–18 years); (2) developed for children, adolescents or caregivers; (3) provided in English or German; (4) operative after download. The quality of eligible apps was assessed with two standardized rating systems (i.e., *Mobile App Rating Scale (MARS)* and *ENLIGHT*) independently by two reviewers.

Results: Overall, the searches revealed 3806 apps, with 15 mental health apps (0.39%) fulfilling our inclusion criteria. The mean overall scores suggested a moderate app quality (MARS: M = 3.59, SD = 0.50; ENLIGHT: M = 3.22, SD = 0.73). Moreover, only one app was evaluated in an RCT. The correlation of both rating scales was high ($r = .936$; $p < .001$), whereas no significant correlations were found between rating scales and user ratings ($p > .05$).

Conclusions: Our results point to a rather poor overall app quality, and indicate an absence of scientific-driven development and lack of methodologically sound evaluation of apps. Thus, future high-quality research is required, both in terms of theoretically informed intervention development and assessment of mental health apps in RCTs. Furthermore, institutionalized best-practices that provide central information on different aspects of apps (e.g., effectiveness, safety, and data security) for patients, caregivers, stakeholders and mental health professionals are urgently needed.

Keywords: mHealth, Internet, Smartphone, Psychotherapy, Children, Adolescent, Anxiety, Depression, Posttraumatic stress disorder

Background

Mental disorders frequently originate in early periods of life [1], and are associated with significant burden and personal suffering [2]. Anxiety, depression and posttraumatic stress disorder are prevalent in children and adolescents, with increasing incidence rates worldwide [3–5]. Without effective and timely treatments, these common

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mental disorders tend to continue into adulthood, with augmented risks to develop further mental disorders and other detrimental outcomes in the long-term [e.g., 6].

Empirically-supported treatment options for common mental disorders in youth (0–18 years) embrace psychotherapy conveyed face-to-face [e.g., 7] and pharmacotherapy [e.g., 8]. In particular, cognitive-behavioral therapy (CBT) has comprehensively documented its effectiveness and acceptability in the treatment of anxiety disorders [9], depression [10, 11] and PTSD in children and adolescents [12]. However, the availability and uptake rates of conventional evidence-based psychotherapies remain low [13], due to different individual and structural barriers, like shortage of mental healthcare supplies, long-waiting times, limitations in mobility, and high treatment costs or fear of stigmatization [14, 15]. Thus, innovative and scalable solutions to lessen this treatment gap are urgently needed; and these novel interventions have to prove their empirical support in terms of various aspects of evidence-based medicine/psychotherapy, such as efficacy and effectiveness, quality or intervention safety.

Internet- and mobile-based interventions (IMIs) hold the potential to lessen existing gaps in mental healthcare [13, 16], as they feature several advantages that might help to overcome some of these obstructions to treatment. First, structural barriers might be reduced, as IMIs can be implemented irrespective of the restraints of space and time [17, 18]. Second, IMIs are deemed to be cost-efficient, as they might be scalable for large numbers of patients [19, 20]. Third, IMIs might also diminish some individual barriers, because these interventions can reduce stigma threat by preserving anonymity, and allow patients to integrate them flexibly into their daily lives at their own pace and individual progress [13, 21]. Furthermore, the digital delivery mode of these novel interventions might be especially appealing for youth, who are frequently familiar and acquainted with the Internet and its applications on mobile devices from an early age [13, 22].

The evidence-base for the efficacy of internet-based psychotherapeutic interventions for some common mental disorders in children and adolescents is documented by several meta-analyses so far [13]. The strongest empirical support can be found for anxiety disorders in youth with effect sizes ranging from 0.30 to 0.77 (standardized mean differences (SMD); 95% CI −0.53 to 1.45) derived from five meta-analyses [23–27]. Furthermore, the efficacy of internet-based interventions for depression in youth is documented by four meta-analyses [23, 24, 27, 28], with effect sizes in the range from 0.16 to 0.76 (SMD; 95% CI −0.12 to 1.12). Aside from this meta-analytical evidence, there is are also preliminary indications that internet-based interventions might be acceptable [29] and cost-effective [30], and hold the potential to extend service supplies within a framework of stepped mental healthcare [29, 31].

Given the efficacy of internet-based psychotherapeutic interventions and the worldwide dispersal of smartphones, mobile health applications (MHA) become more and more appealing as a way to complement or deliver psychotherapeutic support [19]. Recent meta-analyses indicate that also app-based psychotherapeutic interventions are efficacious [32, 33]: For instance, for depressive symptoms (SMD = 0.28, 95% CI 0.21 to 0.36), generalized anxiety symptoms (SMD = 0.30, 95% CI 0.20 to 0.40) [32] or smoking behavior (SMD = 0.39, 95% CI 0.21 to 0.57) [33]. However, studies provide mainly evidence for adults. Of the k = 66 [32] and k = 19 [33] included studies in the meta-analyses on the efficacy of app-based psychotherapeutic interventions, only one focused on youth [34].

The limited evidence on mobile health apps for children and adolescents seems like the more important, as there is already a vast (evidence-free) commercial app market accessible in routine care: In an international cooperation study, the analysis of N = 1.299 commercially available MHA yielded, that 94.8% were not evidence-based [35]. Besides major limitations towards the evidence-base in the app markets, systematic evaluations about the quality of available MHA highlight a high heterogeneity and weak to moderate quality of MHA, especially regarding the engagement of users and information quality [16, 35–38]. Moreover, privacy and security features of MHA available in the app markets have been identified as crucial issues for patients' safety [39, 40].

Hence, it is of utmost importance to evaluate the apps available in the commercial app market to highlight the few high-quality, secure and scientifically evaluated MHA to inform and guide users as well as healthcare professionals. Standardized and reliable instruments like the Mobile Application Rating Scale (MARS) [35, 41, 42] or the ENLIGHT instrument [43] that offer an assessment for quality, privacy features, and evidence-base enable such evaluations. Although previous reviews have systematically evaluated health apps for depression [16] and PTSD [36] in adults, to our knowledge, no such study was conducted relating to mobile-based interventions targeted for common mental disorders in children and adolescents to date. Therefore, this study aimed to systematically evaluate the quality of existing apps that were explicitly designated to address symptoms of anxiety, depression and PTSD in youth, by deploying two established psychometric app rating scales [41–43]. Specifically, we aimed to:

1) systematically evaluate the quality of eligible apps in the European *Google Play Store* and *Apple App Store* regarding user engagement, functionality, aesthetics, and information content;
2) assess privacy and security features;
3) identify theoretical foundations of apps and their respective intervention components;
4) assess the concordance of user ratings and expert ratings.

Methods

Search strategy and inclusion criteria

A systematic search for MHA targeting anxiety, depression and posttraumatic stress disorder (PTSD) in children and adolescents was conducted by using an automatic search engine (webcrawler) that was developed within the mobile health app database project (MHAD; http://mhad.science/ [16, 36]. The webcrawler is a program that searches the app stores for given search terms and automatically extracts the provided information (e.g., app name, app description, user ratings, etc.) from the stores. The functionality and validity of the program has been proven in previous studies [44–46]. For further technical details please see [47].

In the present study, three sets of search terms were used to identify MHA anxiety, depression and PTSD in youth (age range: 0–18 years; Additional file 1). The search terms were derived by a team of psychologists (ASE, MD, YT), among them a licensed psychotherapist for children and adolescents (MD) and an expert for MHA quality (YT; [16, 35, 36]). The systematic searches (both, in English and German) were conducted from April 24th to April 26th, 2019.

After the app identification, a two-step inclusion process was conducted. First all identified apps were screened based on the app title and description regarding the following inclusion criteria: (a) the app was developed to address at least one of the targeted mental disorders, (b) the app was focusing on children and/or their caregivers, (c) the app was available in a language spoken by the authors (German or English), (d) the app was available for download. Second, all remaining apps were downloaded and tested against the criteria a-c again and e) the app was operative. All eligible MHA were included in the current analysis.

Assessment

The Mobile Application Rating Scale (MARS German version [42]) and the ENLIGHT are two standardized and reliable scales to assess the contents and quality of MHA. In the present analysis app characteristics (e.g., app name, price, user-rating) were assessed using the classification site of the standardized MARS [41, 42]. In addition, the classification site was used to assess methods (e.g., mindfulness exercises) and the therapeutic background. Based on previous categorizations [16, 48] therapeutic background was rated as cognitive behavioral therapy (CBT), psychodynamic psychotherapy, behavioral therapy, systemic therapy, third-wave CBT, humanistic therapy, integrative therapy, other, not applicable (N.A.; e.g., mainly psychoeducational content), or mixed (e.g., elements from multiple therapeutic backgrounds and theoretical orientations).

The MARS offers several items to assess privacy and security features (e.g., password protection) on a descriptive level. All included apps were rated by these items. In addition, the ENLIGHT instrument contains four checklists (i.e., privacy, security, credibility, evidence-based score), providing further in-depth assessment domains. For privacy and security, explicit requirements were stated, which are either rated as fulfilled or unfilled. Credibility and evidence-base is rated from very poor to excellent. For further information see [41].

Quality rating

The MARS [41, 42] was used for the quality assessment. With the MARS, MHA quality is rated on a 5-point scale ranging from 1 "inadequate" to 5 "excellent". A total of 19 items on four sub-dimensions were included: (A) engagement (5 items: fun, interest, individual adaptability, interactivity, target group), (B) functionality (4 items: performance, usability, navigation, gestural design), (C) aesthetics (3 items: layout, graphics, visual appeal), and (D) information quality (7 items: accuracy of app description, goals, quality of information, the quantity of information, quality of visual information, credibility, evidence base). The psychometric quality of the MARS is excellent [35, 41, 42]. To assess the evidence base of the included apps, each reviewer conducted a search using Google and Google Scholar (search terms: app name, efficacy, effectiveness, observation study, study, evaluation, usability) and searched on the website of the app and app provider for information on conducted studies. Based on the search results the evidence items was rated as NA ("The app has not been trialled/tested"), 1 ("The evidence suggests the app does not work"), 2 ("App has been trialled (e.g., acceptability, usability, satisfaction ratings) and has partially positive outcomes in studies that are not randomised controlled trials (RCTs), or there is little or no contradictory evidence"), 3 ("App has been trialled (e.g., acceptability, usability, satisfaction ratings) and has positive outcomes in studies that are not RCTs, and there is no contradictory evidence"), 4 ("App has been trialled and outcome tested in 1–2 RCTs indicating positive results"), or 5 ("App has been trialled and outcome tested

in > 3 high quality RCTs indicating positive results") [41]. In addition to the four objective quality scales, the MARS contains two subjective subscales: (E) subjective quality (4 items: recommendation, frequency of use, willingness to pay, overall star-rating) and (F) perceived impact (6 items: awareness, knowledge, attitudes, intention to change, help-seeking, behavioural change).

In addition to the MARS, the ENLIGHT instrument was applied, since it provides information on additional dimensions (e.g., therapeutic alliance). ENLIGHT's items are rated on a 5-point scale ranging from 1 "very poor" to 5 "very good". In total ENLIGHT covers 28 items on seven sub-dimensions: (a) usability (3 items), (b) visual design (3 items), (c) user engagement (5 items), (d) content (4 items), (e) therapeutic persuasiveness (7 items), (f) therapeutic alliance (3 items), and (g) general subjective evaluation (3 items). The internal consistency of ENLIGHT is excellent [43].

Rater training

The quality rating was conducted by two independent reviewers (ASE, SE). All reviewers completed online training for the MARS before the quality assessment (https://www.youtube.com/watch?v=5vwMiCWC0Sc; last updated on September 6, 2021). For the ENLIGHT instrument, no free online training is available. Instead, reviewers were trained in using the ENLIGHT by an researcher with prior experience and expertise in app quality assessment (YT; [16, 35, 36]. After the instruction, several test apps were rated by both reviewers (ASE, SE) and ratings were discussed between the reviewers and instructor (YT) to complete the training phase. The excellent inter-rater reliability between the trained reviewers for the MARS (ICC = 0.87, 95% CI 0.84 to 0.90) and the inter-rater reliability for the ENLIGHT (ICC = 0.75, 95% CI 0.65 to 0.83) highlight that the training was successful.

Data analyses

MHA characteristics, therapeutic backgrounds, methods, and privacy and security features were analyzed descriptively. As a measure of agreement between the trained reviewers, intra-class correlation (ICC) was calculated for the dimensional quality assessment [49]. An ICC above 0.75 was defined as a satisfactory agreement between the reviewers [50]. The ratings of both reviewers were pooled. After pooling, means and standard deviations were calculated for all quality dimensions of the MARS and ENLIGHT. The associations between user ratings (star-rating in the stores: 5-point rating from 1 star to 5 stars) and experts' quality ratings with the MARS and ENLIGHT were investigated by correlation analysis. For correlation analysis, an alpha level of 5% was defined. Holm correction for multiple testing was applied [51]. Missing values were excluded list-wise.

Results

Search and app characteristics

In total, 3806 MHA were identified (Apple App Store = 2658, Play Store = 1148). After the eligibility check, 15 MHA were included. All MHA were developed for Apple devices and n = 7 MHA were also available on Android. The inclusion process is summarized in Fig. 1.

Most MHA (n = 9, 60%) were from the category *Health and Fitness*, followed by n = 6 (40%) from the category *Medicine*. *Lifestyle* (n = 3), *Education* (n = 2) and *social networks* (n = 1) were represented categories as well. Of the 15 included MHA, two targeted depression, four anxiety, three PTSD. The remaining six targeted mixed symptoms of anxiety, depression and PTSD. Most MHA were freely available (n = 9, 60%). Prices of the six fee-based MHA (40%) ranged from 1.09 EUR to 10.99 EUR. On average, users rated the included MHA moderate to good (M = 3.6; SD = 1.04); three MHA were not rated by users. MHA characteristics are summarized in Table 1.

The investigation of methods provided by the included MHA yielded 18 different features. Most frequently, MHA provided information (n = 7) and offered psychoeducational advice (n = 7). A total of n = 6 MHA (40%) included a monitoring function. MHA also included therapeutic functions. For an aggregated overview of all functions, see Fig. 2.

In four apps the used functions and exercises were taken from multiple therapeutic backgrounds. A clear CBT focus was observed in two MHA, while at least some CBT elements (including third-wave CBT) were present in six of the MHA. Interestingly, a total of three apps incorporated the contact to a therapist or coach, which may lead to different therapeutic backgrounds and applied techniques depending on the assigned therapist or coach. An MHA-specific summary of the provided functions as well as the therapeutic background of the MHA is provided in Table 2.

Privacy, security and evidence

Of all 15 included MHA, n = 6 (40%) offered password protection, n = 4 (27%) required a log-in, n = 7 (47%) had a visible privacy policy, and n = 7 (47%) had an imprint. Consent to data collection was required in an active form by n = 5 (33%) MHA and in a passive form by n = 8 (53%), n = 1 informed about conflicts of interest/financial background. An emergency function was provided by n = 2 (13%) MHA. The ENLIGHT checklist evaluation of

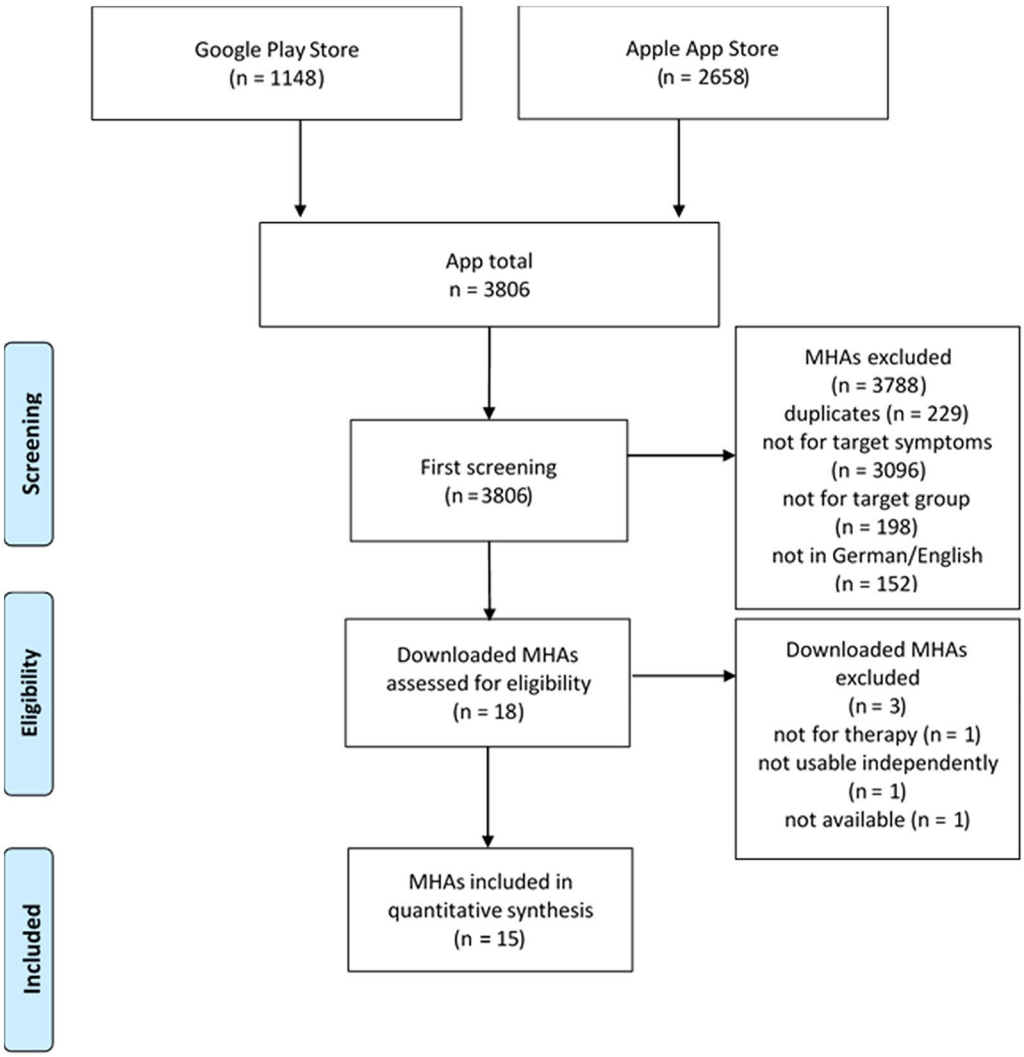


Fig. 1 Flow-chart of the in- and exclusion process

privacy, security, credibility, and evidence-base is summarized in Table 3.

In addition to the ENLIGHT checklist, evidence-base was assessed by MARS with the item "Has the app been trialled/tested?". The assessment revealed, that only a single MHA ("iChill") has been evaluated and outcome tested in an RCT.

Quality rating

MARS

The overall average quality of MHA was M = 3.59 (SD = 0.50). Quality ratings of the four sub-dimensions resulted in: engagement M = 3.34 (SD = 0.76), functionality M = 3.81 (SD = 0.49), aesthetics M = 3.78 (SD = 0.63), information quality M = 3.42 (SD = 0.68). The subjective quality was M = 3.13 (SD = 0.62) and the perceived impact M = 2.80 (SD = 0.75). Detailed information can be obtained from Table 4.

ENLIGHT

The overall quality was M = 3.22 (SD = 0.73). Quality ratings of the sub-dimensions yielded: usability M = 3.84 (SD = 0.39), visual design M = 3.72 (SD = 0.55), user engagement M = 3.27 (SD = 0.80), content M = 3.34 (SD = 0.72), therapeutic persuasiveness M = 2.34 (SD = 0.78), therapeutic alliance M = 2.56 (SD = 1.08), general subjective evaluation M = 3.34 (SD = 0.83). For detailed information see Table 1.

Table 1 App characteristics

Name	Version	Store	User rating	Number of ratings	Category	Price
Anxiety Coach	1.3.6	Apple	2.5	8	Health & fitness	5,50 EUR
BoosterBuddy	1.6	AppleGoogle Play	4.4	27	Health & fitness, lifestyle	Free
Braineka Panic Attacks	2	Apple	NA	0	Medicine	3,49 EUR
ClearFear	1.3	AppleGoogle Play	4.3	12	Healt & fitness	Free
Depression Test and Training	3.5.10	Apple	3.6	5	Medicine,Health &Fitness	In-App purchases
EMDR Therapy	0	Apple	4.0	1	Medicine	10,99 EUR
eReading: Sam	0	Apple	1.0	1	Education	2,29 EUR
FearShrinker	1.3	Apple	NA	0	Medicine	6,99 EUR
iChill	2.1	AppleGoogle Play	4.1	13	Health & fitness	Free
iPrevail	3.6.8	AppleGoogle Play	3.3	36	Health & fitnesssocial networks	In-App purchases
Kids' Grief	1.5	Apple	NA	0	Lifestyle	1,99 EUR
Parent-Guide	1.0.0	AppleGoogle Play	5.0	1	Education medicine	Free
Talkspace OnlineTherapy	8.53.03	AppleGoogle Play	3.6	11	Health & fitnessmedicine	In-App purchases
Teen Counseling	7.1	AppleGoogle Play	4.1	82	Health &fitness, lifestyle	In-App purchases
The Emotion Diary	2.3	Apple	3.3	3	Health & fitness, lifestyle	In-App purchases

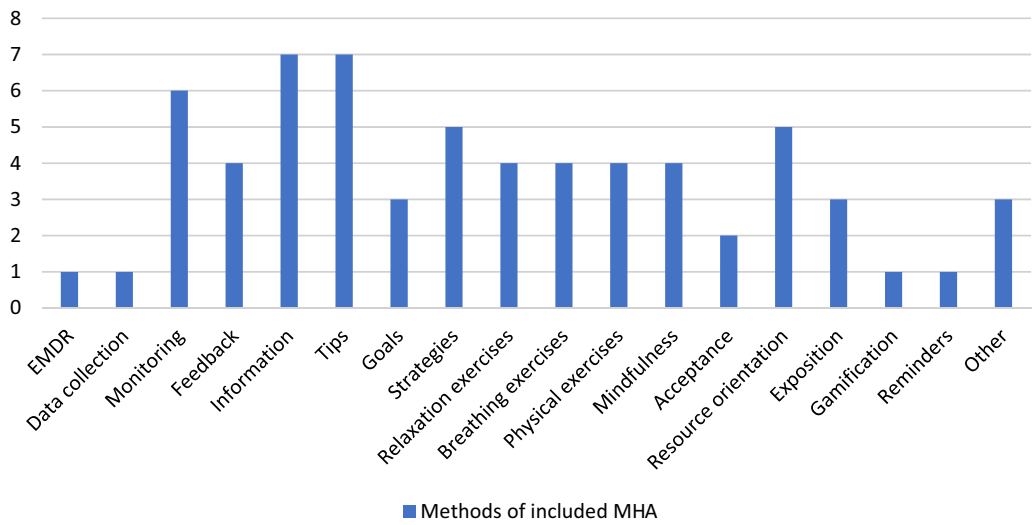


Fig. 2 Methods and functions of included MHA

Associations between measures

Correlation between the overall MARS and ENLIGHT were high ($r = .936$, $p < .001$). No significant correlations between either MARS or ENLIGHT with user star rating were found ($p > .050$).

Discussion

To the best of our knowledge, this is the first study that systematically evaluated the quality of available apps that were denoted to tackle symptoms of anxiety, depression and PTSD in youth. Although our systematic searches yielded in a high number of initial hits, only a very small fraction of apps (0.39%) fulfilled our eligibility criteria and were independently assessed with two established app rating scales. Overall, the results point to a mediocre quality of the 15 included apps, and most importantly, to a widespread absence of rigorous scientific evaluations of apps in RCT-studies.

Our quality ratings are in line with the results of previous systematic evaluations deploying the same rating

Table 2 Content summary

Name	Keywords	Methods and functions	Therapeutic background
Anxiety coach	Anxiety disorder, cognitive behavioral therapy, self-confidence	Monitoring, feedback, information, tips, goals, exposition	CBT
BoosterBuddy	Mental health, coping, establishing positive behavior	Monitoring, feedback, information, tips, goals, strategies, relaxation, mindfulness, acceptance, resource orientation, reminders	Mixed (with elements of CBT, behavioral therapy, third-wave CBT)
Braineka Panic Attacks	Panic attacks, anxiety disorder, exposition	Relaxation, breathing exercises, exposition	Mixed (with elements of CBT, third-wave CBT, behavioral therapy)
ClearFear	Anxiety disorder, resilience, relaxation	Tips, relaxation, breathing exercises, physical exercises, resource orientation	CBT
Depression test and training	Depression, diagnosis, cognitive training	Data collection, monitoring, feedback, information, strategies, gamification	Other (Neuropsychology)
EMDR therapy	support trauma therapy, EMDR	EMDR	Other (EMDR)
eReading: Sam	narrative, life with PTSD, trauma	Information, strategies, breathing exercises, physical exercises	N.A. (Psychoeducation)
FearShrinker	Anxiety disorder, strategies, coping	Monitoring, feedback, information, tips, goals, strategies, relaxation, breathing exercises, physical exercises, exposition	Mixed (with elements of CBT, behavioral therapy)
iChill	Resilience-model, self help, stress, trauma	Monitoring, physical exercises, mindfulness, acceptance, resource orientation	Other (Community Resilience Model)
iPrevail	Community support, anonymous chat, peer group	Tips	Various depending on therapist/coach
Kids' grief	Advice for parents, coping with grief, support	Information, tips, resource orientation	N.A. (Psychoeducation)
Parent-guide	Traumatic event, strategies, security	Information, tips, strategies, mindfulness, other	N.A. (Psychoeducation)
Talkspace online therapy	"Match" with an online therapist	Other	Various depending on therapist/coach
Teen counseling	"Match" with an online therapist	Other	Various depending on therapist/coach
The emotion diary	Positive psychology, diary, tracking	Monitoring, mindfulness, resource orientation	Mixed (with elements of positive psychology and third-wave CBT)

scales on apps for various health conditions and application areas (e.g., depression, PTSD, pain, rheumatism, physical activity, weight management [16, 36, 38, 44–46, 52–54]), all indicating medium overall app qualities with the MARS and ENLIGHT scales. In our study, the categories with the highest ratings were aesthetics and functionality (M = 3.78; M = 3.81), followed by information quality (M = 3.42) and engagement (M = 3.34). Also corresponding to previous studies [16, 36], the most often deployed therapeutic background for health apps was CBT, with various intervention components applied such as psychoeducation, relaxation techniques, mindfulness, exposure or monitoring/tracking.

However, and most importantly, a common deficiency of MHA is the absence of empirical investigations on their efficacy [16, 36, 55], which represents a major limitation and confines further quality aspects in our view. Considering this lack of empirical support, it seems like a minor issue that youth, caregivers and mental health professionals are hardly able to disentangle the overabundance of available apps and to distinguish therapeutic relevant apps from those that are irrelevant for their health-related intentions [56]. Moreover, our results suggest that app users might not be able to sufficiently appraise the quality of available apps, given the discrepancy of expert and user ratings, which is consistent with findings from other studies [16]. Thus, it seems necessary that objective and scientifically-based expert ratings are publicly available, in order to enable patients to make informed and guided decisions about MHA in particular, and psychotherapeutic interventions in general, advocating evidence-based mental healthcare.

Next to several strengths (including the resort to established scientifically validated app rating scales, the focus on prevalent mental disorders and comprehensive scope on apps with divergent theoretical backgrounds), there are several limitations that ought to be considered when interpreting the findings of this current study. First, the search strategy embraced only available apps in the European *Google Play* and *Apple App* stores, and therefore the

Table 3 Checklist summary ENLIGHT

App	Privacy	Security	Credibility	Evidence-based score
FearShrinker	X	X	NA	Very poor
ClearFear	X	X	Poor	Very poor
Anxiety Coach	X	X	Fair	Very poor
Braineka Panic Attacks	X	X	Fair	Very poor
Depression Test und Training	X	X	Fair	Very poor
Kids' Grief	X	X	NA	Very poor
Parent-Guide	X	X	Good	Very poor
eReading: Sam	X	X	NA	Very poor
EMDR Therapy	X	X	NA	Very poor
BoosterBuddy	X	X	Fair	Very poor
Teen Counseling	X	X	Fair	Very poor
Talkspace Online Therapy	X	X	Good	Very poor
iChill	X	X	Fair	Fair
iPrevail	X	X	Poor	Very poor
The Emotion Diary	X	X	NA	Very poor

X represents, that requirements by the ENLIGHT instrument were not met. Credibility was rated as NA, if credibility could not be accounted for (see ENLIGHT [43])

results might not be representative for other outlets and app stores. Second, the rapidly evolving dynamics of the app market [16, 36, 57] might have led to the omission of novel apps as well as updates of included apps, and that some of the apps might not be accessible anymore. Third, since the two rating scales were not designed for the specificities of child and adolescent psychotherapy (i.e., addressing relevant developmental issues), ratings of youth MHA should be interpreted with caution—especially in regard to the domains of functionality and information content. Therefore, it would be a significant scientific advancement, if specific MHA rating scales were available and psychometrically evaluated for mobile-based interventions for common mental disorders in youth. Fourth and foremost, quality ratings can never be sufficient to inform clinical practice and treatment approaches alone, since efficacy and effectiveness studies are the core and gold-standard of evidence-based mental healthcare.

Accordingly, the most important future direction and imperative necessity for the advancement of MHA, is their methodological sound and rigorous evaluation in randomized controlled trials (or novel alternative evaluation frameworks to MHA)—since only one app was subject to an efficacy study, with sobering non-significant findings [58]. Without comprehensive knowledge on their (non-)efficacy and intervention safety, these novel applications ought not to be part in routine mental healthcare. However, some stakeholders might compromise some established standards of evidence-based medicine and advocate the evaluation of MHA in routine clinical care – without prior information on their efficacy and harmlessness. This debatable procedure can

Table 4 MARS rating

App	Engagement	Functionality	Aesthetics	Information quality	Overall	Subjective quality	Perceived impact
FearShrinker	4.4	4.50	4.33	3.33	4.14	3.75	3.17
ClearFear	4.4	4.13	4.33	3.42	4.07	3.63	3.42
Anxiety Coach	3.3	3.5	3.33	3.70	3.46	3.13	3.33
Braineka Panic Attacks	2.9	3.88	4.17	3.58	3.63	2.75	2.08
Depression Test und Training	3.5	3.88	4.50	3.71	3.90	2.88	2.33
Kids' Grief	2.8	3.25	2.83	3.50	3.10	3.00	3.58
Parent-Guide	2.8	4.25	4.00	3.60	3.66	3.38	2.75
eReading: Sam	3.5	3.50	3.50	2.33	3.21	3.25	3.92
EMDR Therapy	2.9	2.50	3.17	3.00	2.89	2.00	1.00
BoosterBuddy	4.5	4.13	4.50	4.13	4.31	4.00	3.42
Teen Counseling	3.9	4.25	4.50	2.92	3.89	3.88	3.00
Talkspace Online-Therapy	3.6	4.00	4.00	5.00	4.15	3.75	2.83
iChill	1.9	3.63	3.33	3.67	3.13	2.88	2.42
iPrevail	3.6	3.88	3.50	3.30	3.57	2.13	2.75
The Emotion Diary	2.1	3.88	2.67	2.17	2.70	2.50	2.00
	3.34 (SD = 0.76)	3.81 (SD = 0.49)	3.78 (SD = 0.63)	3.42 (SD=0.68)	3.59 (SD = 0.50)	3.13 (SD = 0.62)	2.80 (SD = 0.75)

Table 5 ENLIGHT rating

App	Usability	Design	User engagement	Content	Therapeutic persuasiveness	Therapeutic alliance	Subjective evaluation
FearShrinker	4.83	4.33	4.20	3.75	3.21	3.33	3.83
ClearFear	4.00	4.83	4.10	4.00	3.29	3.00	4.33
Anxiety Coach	3.50	3.33	3.10	3.75	3.21	1.67	3.33
Braineka Panic Attacks	4.17	3.83	2.50	3.50	2.14	2.83	3.00
Depression Test und Training	4.00	4.17	3.70	3.38	2.70	2.17	3.50
Kids' Grief	3.67	2.83	2.50	3.75	2.00	2.17	3.17
Parent-Guide	4.00	3.83	2.20	3.88	2.14	2.67	3.33
eReading: Sam	3.50	3.67	2.80	3.50	1.64	3.50	3.67
EMDR Therapy	3.50	3.33	2.40	2.00	1.50	1.00	2.17
BoosterBuddy	4.00	4.33	4.70	4.38	4.00	4.50	4.33
Teen Counseling	4.00	4.00	3.80	3.75	NA[1]	NA[1]	4.83
Talkspace Online Therapy	4.00	3.67	3.80	3.25	NA[1]	NA[1]	3.67
iChill	3.33	3.33	2.50	2.75	1.93	1.67	2.17
iPrevail	3.83	3.33	3.90	2.50	2.17	3.83	2.83
The Emotion Diary	3.33	3.00	2.80	2.00	1.67	1.00	2.00
	3.84 (SD = 0.39)	3.72 (SD = 0.55)	3.27 (SD = 0.80)	3.34 (SD = 0.72)	2.43 (SD = 0.78)	2.56 (SD = 1.08)	3.34 (SD = 0.83)

[1] The MHAs Teen Counseling and Talkspace offer connections to licensed/trained counselors and therapists. Therapeutic persuasiveness and alliance may vary depending on the assigned counselor/therapist. For a reliable assessment multiple counselors and therapists would have been necessary, which was not possible within this study (→ NA)

be observed in the health sector in Germany, where clinicians and healthcare providers are currently entitled to prescribe apps, with the intention of the German health ministry and certifying agency (i.e., BfArM) to gain an evaluation of their effectiveness post-hoc (with app providers contributing these data themselves). As such, this development might bring several risks for individual patients (e.g., non-detected and unknown side effects, adverse events, or deterioration) and might contribute to an erosion of well-established standards of evidence-based medicine in general. This concern is also nourished by the massive commercialization of the app market and limited resources in healthcare globally, raising further methodological and ethical questions [59, 60]. Thus, the adherence to well-established standards of good clinical practices as well as scientific-based intervention evaluation should be urgently applied for MHA [61], similar as it is largely the case for internet-based interventions and conventional psychotherapies offered face-to-face. Recommendations for quality criteria and standards for MHA are available, and can complement efficacy-/effectiveness studies on MHA in RCTs [62, 63]. Furthermore, the development of MHA needs to get theoretically and empirically informed, since dismantling and additive design studies are largely pending in mobile-based interventions [18], and the resort to theoretically deduced and evidence-based intervention components is a critical step to build efficacious interventions that induce essential mechanisms of therapeutic change enabling improved outcomes [64].

Taken together, our study indicates that MHA for youth possess a rather small quality and, more importantly, are insufficiently evaluated concerning their efficacy, impeding widespread conclusions and recommendations for clinical practice and healthcare policies so far. Therefore, it is of utmost importance that patients and stakeholders are thoroughly and scientifically informed about this limited evidence base and the current deficiencies and restraints of MHA for youth. Information platforms offered by (non-profit) organizations, like www.mhad.science (last updated September 6, 2021) or https://onemindpsyberguide.org/ (last updated September 6, 2021), that gather and provide scientific knowledge on central aspects of digital health interventions (e.g., effectiveness, acceptability, quality, safety, or data security) in a balanced and unbiased way, are one important contribution for the evidence-based information and empowerment of patients seeking advice and help for their mental health resolutions.

Conclusions

This study systematically evaluated the quality of MHA for anxiety, depression and PTSD in youth. The results revealed a moderate overall app quality and point to a significant lack of empirically-informed intervention development, as well as an absence of rigorous studies to investigate the efficacy of apps that are currently offered in major marketplaces. Hence, future high-quality research is urgently needed, to advance and evaluate MHA, all contributing to the augmentation and evidence-based utilization of digital health interventions. Furthermore, non-profit provisions of scientifically-based information on essential aspects of apps are urgently required to enable informed and balanced treatment choices for patients, caregivers and stakeholders in mental health.

Supplementary Information

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Additional file 1. Search terms.

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Authors' contributions
MD, YT, YT, HB, EMM, LS designed the trial and initiated this study. ASE and SE conducted the MARS ratings supervised by MD and YT. MD and YT wrote the first draft of the manuscript. All authors revised the manuscript. All authors read and approved the final manuscript.

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Availability of data and materials
Data will be made available to researchers who provide a methodologically sound proposal, not already covered by other researchers. All requests should be directed to the corresponding author. Data requestors will need to sign a data access agreement. Provision of data is subject to data security regulations. Support depends on available resources.

Declarations

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Not applicable.

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No potential competing interests are reported by the authors.

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Part II

Towards an integrative conceptual model of the mechanisms of change in digital interventions

Part II comprises the following chapter, published as:

Chapter 5. Domhardt, M., & Baumeister, H. (2021). Wirkfaktoren und Veränderungsmechanismen digitaler psychotherapeutischer Interventionen. *Psychotherapeut, 66* (5), 414-423. https://doi.org/10.1007/s00278-021-00525-2

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Chapter 5

Wirkfaktoren und Veränderungsmechanismen digitaler psychotherapeutischer Interventionen

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Wirkfaktoren und Veränderungsmechanismen digitaler psychotherapeutischer Interventionen

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In diesem Beitrag

- **Wirkungsweisen digitaler Psychotherapie – Vorschlag eines Modells und beispielhafte aktuelle Evidenz zu depressiven Störungen**
  Komponenten internet- und „mobile"-basierter Interventionen zur Therapie von Depression • Mediatoren und Veränderungsmechanismen • Engagement • Therapeutische Begleitung (Guidance) und „supportive accountability" • Selbsthilfeinterventionen • Moderatoren
- **Von der theoretischen Konzeptualisierung hin zur empirischen Fundierung**

Zusammenfassung

Obgleich die Wirksamkeit internet- und „mobile"-basierter Interventionen für verschiedene psychische Störungen zwischenzeitlich als gut belegt anzusehen ist, existiert bislang wenig gesichertes Wissen zu spezifischen Wirkungsweisen digitaler Psychotherapie. Im vorliegenden Beitrag werden zunächst zentrale Begriffe und Methoden der Psychotherapieprozessforschung erörtert (u. a. allgemeine und spezifische Wirkfaktoren, Komponentenstudien, Mediatoren und Veränderungsmechanismen), um darauf aufbauend ein integratives psychologisches Modell über die möglichen Wirkungsweisen digitaler Psychotherapie vorzustellen. Die einzelnen Bestandteile des Modells werden anhand der empirischen Evidenz beispielhaft zu depressiven Störungen diskutiert, mit einem Ausblick hinsichtlich zentraler Forschungsdesiderate.

Schlüsselwörter
Internet · „Mobile health" · Digitale Gesundheitsintervention · Veränderungsmechanismus · Therapeutische Prozesse

Zusatzmaterial online

Zusätzliche Informationen sind in der Online-Version dieses Artikels (https://doi.org/10.1007/s00278-021-00525-2) enthalten.

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Evidenzbasiertes Wissen über die therapeutisch-aktiven Wirkfaktoren und Veränderungsmechanismen von Psychotherapie – im vorliegenden Beitrag von digitalen psychotherapeutischen Interventionen – kann maßgeblich dazu beitragen, diese und auch konventionelle Interventionen empirisch fundiert weiterzuentwickeln sowie Verläufe und Ergebnisse von Psychotherapien zu optimieren. Fundierte Psychotherapieprozessforschung setzt jedoch die Anwendung einheitlicher Begriffsbezeichnungen und -operationalisierungen voraus. Die vorliegende Arbeit leistet einen Beitrag dazu, diese Voraussetzungen zu schaffen, um darauf aufbauend mithilfe eines integrativen psychologischen Modells zu depressiven Störungen das Wissen über mögliche Wirkungsweisen digitaler Psychotherapie zu erweitern.

Hintergrund

Die prototypische Publikation über die Wirkfaktoren und Veränderungsmechanismen von Psychotherapie beginnt häufig mit der Ausführung, dass die Wirksamkeit eines psychotherapeutischen Verfahrens zwar gut belegt, das Wissen über die jeweiligen Wirkungsweisen dahingegen begrenzt ist (Lorenzo-Luaces und DeRubeis 2018). Eine ähnliche Aussage kann zwischenzeitlich auch für verschiedene Formen digitaler psychotherapeutischer Interventionen getroffen werden. So liegen mittlerweile zahlreiche metaanalytische Wirksamkeitsnachweise für internetbasierte (z. B. Domhardt et al. 2020; Königbauer et al. 2017; Reins et al. 2020) und Smartphone-App-basierte Interventionen (z. B. Terhorst et al. 2018; Weisel et al. 2019; Firth et al. 2017; Linardon et al. 2019) bei verschiedenen psychischen Störungen, insbesondere Angststörungen

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und Depression, vor. Das Wissen um die Wirkfaktoren (Domhardt et al. 2019) und Veränderungsmechanismen (Domhardt et al. 2021b) von digitalen psychotherapeutischen Interventionen fällt jedoch im Vergleich zum Wissenstand nach Dekaden der Therapieprozessforschung von klassischer Psychotherapie vor Ort freilich noch geringer aus und beginnt, sich gerade erst zu entwickeln.

Evidenzbasiertes Wissen über die therapeutisch-aktiven Wirkfaktoren und Veränderungsmechanismen von Psychotherapie – in ihrer jeweiligen Ausführungsmodalität – ist u. a. deshalb von besonderer Bedeutung, da es maßgeblich dazu beitragen kann, psychotherapeutische Interventionen empirisch fundiert weiterzuentwickeln sowie darüber Therapieverläufe und Behandlungsergebnisse optimieren zu können (Domhardt et al. 2019, 2021b; Kazdin 2007). Die aufkommenden Möglichkeiten einer digitalisierten Psychotherapieprozessforschung könnten wertvolle Erkenntnisse zeitigen, die gleichermaßen für digitale und auch konventionelle Formen von Psychotherapie relevant sein dürften (Domhardt et al. 2021c). Dafür erscheint es jedoch unerlässlich, einheitliche Begriffsbezeichnungen und -operationalisierungen zu erlangen, und verschiedene methodische Herausforderungen zu lösen, die das Feld der Psychotherapieprozessforschung lange Zeit beeinträchtigt haben. Im vorliegenden Beitrag werden demnach zunächst zentrale Konzepte und Methoden der Psychotherapie(prozess)forschung erörtert, daraufhin der aktuelle Stand der Forschung zur Wirkungsweisen digitaler Psychotherapie anhand eines Modells – mit einem besonderen Fokus auf internet- und „mobile"-basierte Interventionen (IMI) für Depression – beispielhaft beschrieben, bevor mit einem Ausblick und Fazit geschlossen wird.

Konzepte und Methoden der Psychotherapieprozessforschung

Erkenntnisse über die Wirkungsweisen von psychotherapeutischen Interventionen können insbesondere aus Komponentenstudien und Mediationsanalysen gewonnen werden. Dabei zielen Komponentenstudien darauf ab, den differenziellen Einfluss einzelner Interventionskomponenten auf die Wirksamkeit einer Behandlung zu bestimmen, um darüber zum Verständnis beizutragen, *wodurch* (d. h. durch welche Bestandteile) eine Therapie wirkt (Cuijpers et al. 2017, 2019b; Domhardt et al. 2019). Im Rahmen von Komponentenstudien werden psychotherapeutische Interventionen, die mehrere Bestandteile/Module aufweisen, mit Variationen der gleichen Intervention verglichen, in denen entweder eine Interventionskomponente ausgelassen („dismantling studies") oder zum vollständigen Behandlungspaket hinzugefügt wird („additive design studies"). Sofern solch eine Komponentenstudie als randomisierte klinische Studie („randomized controlled trial", RCT) durchgeführt wird, kann sie robustes Wissen um die Effektstärken einzelner Interventionskomponenten erbringen und kausale Inferenzschlüsse zur differenziellen Wirksamkeit einzelner Therapiebestandteile ermöglichen (Cuijpers et al. 2017; Domhardt et al. 2019). Die therapeutisch-wirksamen Komponenten können sodann als aktive Bestandteile („active ingredients") einer Therapie betrachtet und ferner in spezifische oder allgemeine Wirkfaktoren psychotherapeutischer Interventionen unterschieden werden (Mulder et al. 2017). Spezifische Wirkfaktoren sind zumeist mit den jeweiligen therapeutischen Techniken und Strategien gleichzusetzen, die für einen bestimmten therapeutischen Ansatz charakteristisch sind, auf einem spezifischen psychotherapeutischen Verfahren und deren theoretischen Konzeption fußen und/oder von einem störungsspezifischen ätiologischen Modell abgeleitet werden. Als Beispiele für spezifische Wirkfaktoren können die kognitive Umstrukturierung und Verhaltensaktivierung innerhalb der kognitiven Verhaltenstherapie (KVT) oder Übertragungs- und Widerstandsdeutung bei tiefenpsychologischen Therapieansätzen genannt werden. Allgemeine Wirkfaktoren treten dahingegen therapieverfahrenübergreifend in psychotherapeutischen Interventionen auf, unabhängig von der theoretischen Orientierung und dem jeweiligen therapeutischen Ansatz. Als prototypische Beispiele für allgemeine Wirkfaktoren werden häufig die therapeutische Allianz oder die Induktion von (Besserungs-)Erwartungen angeführt. Derweil entwickelt sich die jahrzehntewährende Debatte über die relative Bedeutsamkeit und unterschiedlichen Rollen von spezifischen und allgemeinen Wirkfaktoren zu einem weithin anerkannten Konsens, dass beide Wirkfaktorenklassen – resp. deren Wechselwirkungen – zur Effektivität psychotherapeutischer Interventionen beitragen (Mulder et al. 2017; Pfammatter und Tschacher 2016).

Indes geben die Befunde aus Komponentenstudien nicht notwendigerweise darüber Aufschluss, *wie* (d. h. auf welche Weise) psychotherapeutische Interventionen wirken, und welche Prozesse innerhalb von Patient*innen zu einer therapeutischen Veränderung führen. Diesen Fragestellungen kann mithilfe von Mediationsanalysen nachgegangen werden (Kazdin 2007), die mitunter als Quintessenz der Psychotherapieprozessforschung angesehen werden können. Mediatoren wie Selbstwirksamkeit oder funktionale Kognitionen sind intervenierende Variablen, die den statistischen Zusammenhang zwischen einer psychotherapeutischen Intervention und dem Behandlungsergebnis vermitteln (Kazdin 2007) und dabei auf mögliche Veränderungsmechanismen hinweisen, durch die eine Intervention ihre Effekte erzielt (Kraemer et al. 2002). Dabei ist es wichtig zu betonen, dass Mediatoren einerseits mit dem Veränderungsmechanismus kongruent und identisch sein können; andererseits können Mediatoren jedoch lediglich stellvertretend für eine oder mehrere andere Variablen sein, die den angenommenen Veränderungsmechanismus tatsächlich erklären (Kazdin 2007). Dabei können diese sog. Proxy-Variablen zu einer gegebenen Zeit bekannt oder unbekannt sein, und im Rahmen einer Untersuchung erhoben oder nicht erhoben worden sein – wodurch sich wiederum das Ausmaß und die Grenzen von kausalen Inferenzschlüssen ergeben (Ohlsson und Kendler 2019). Infolgedessen ist es im Kontext der Psychotherapieprozessforschung erstrebenswert, dass Mediatoren (1) theoretisch fundiert (d. h. konzeptuell einen plausiblen Veränderungsmechanismus darstellen, der durch eine Interventionskomponente induziert wird), (2) a priori definiert und operationalisiert sowie (3) im Vergleich zu anderen bekannten, potenziellen Mediatoren eva-

luiert werden (Kazdin 2007; Kraemer et al. 2002).

Moderatoren sind dahingegen Variablen (wie beispielsweise Geschlecht, Alter oder Symptomschwere), die das Ausmaß oder die Richtung des Zusammenhangs zwischen einer Intervention und einem Behandlungsergebnis beeinflussen. Sie geben darüber Aufschluss, bei welchen Personen(gruppen) mit ähnlichen Merkmalen und unter welchen Umständen eine Behandlung differenzielle Effekte erzielt (Kazdin 2007; Kraemer et al. 2002). Damit können Moderatoren wichtige Beiträge zur Personalisierung von Psychotherapie leisten. Variablen, die als Moderatoren infrage kommen, müssen einer Intervention zeitlich vorgeordnet und von ihr unabhängig sein; wohingegen Variablen, die sich als Mediatoren qualifizieren, chronologisch immer nach der Initiierung einer Intervention (bzw. einzelnen Komponenten im Rahmen einer Behandlung) aktiv werden und mit der Intervention korreliert sein müssen. Moderatoren können also darauf hinweisen, dass verschiedene Veränderungsprozesse in unterschiedlichen Personen(gruppen) vorherrschend sind („moderierte Mediation"), stellen jedoch per se keinen therapeutischen Veränderungsmechanismus dar (Kraemer et al. 2002; Kazdin 2007).

Als bekannteste Methode zur statistischen Evaluation von Mediatoren gilt das von Baron und Kenny 1986 in einem wegweisenden Artikel vorgestellte Verfahren. Im Rahmen dieser „causal steps approach" genannten Vorgehensweise werden 4 aufeinander aufbauende Bedingungen mithilfe von Regressionsanalysen geprüft (Baron und Kenny 1986), um zu zeigen, dass ein Mediator *M* den Effekt einer unabhängigen Variable *X* (die Intervention) auf eine abhängige Variable *Y* (das Ergebnis) vermittelt. Obgleich der Ansatz der Mediationsanalyse nach Baron und Kenny (1986) nach wie vor in verschiedenen wissenschaftlichen Disziplinen häufig angewendet wird, weist diese Vorgehensweise verschiedene Einschränkungen auf, die insbesondere in der Psychotherapieprozessforschung zum Nachteil gereichen. So ist etwa die statistische Teststärke beim Causal steps approach gering, und es sind sowohl hohe Fallzahlen wie auch beträchtliche Behandlungseffekte erforderlich, um indirekte Effekte (Mediationseffekte) nachweisen zu können (MacKinnon et al. 2007). Diese Voraussetzungen sind jedoch in der Psychotherapieprozessforschung nur selten gegeben (z. B. bei Depression; Lemmens et al. 2016). Außerdem können komplexe Mediationsmodelle mit multiplen Mediatoren mithilfe des Ansatzes nach Baron und Kenny nur schwer dargestellt werden, da jeder indirekte Effekt unabhängig voneinander geschätzt werden muss (MacKinnon et al. 2007). Es ist jedoch anzunehmen, dass nicht nur ein, sondern mehrere Veränderungsmechanismen – unabhängig voneinander oder sich gegenseitig beeinflussend – in psychotherapeutischen Interventionen beteiligt sind (Cuijpers et al. 2019b; Domhardt et al. 2019). Daher sollten Modelle mit mehreren Mediatoren methodisch angemessen evaluiert werden. Darüber hinaus ist der Causal steps approach nur anwendbar, wenn verschiedene Interventionsbedingungen/Therapieansätze auch unterschiedliche Behandlungsergebnisse aufweisen. Bei Betrachtung des allgemeinen Befundes, dass verschiedene psychotherapeutische Interventionen gleichermaßen effektiv in der Behandlung, von etwa depressiven Störungen sind (z. B. Cuijpers et al. 2019a), wird ein bedeutsamer Nachteil des mediationsanalytischen Ansatzes nach Baron und Kenny deutlich. Gerade Kenntnisse darüber, ob diese gleichermaßen wirksamen Behandlungsansätze ihre Effektivität durch ähnliche/identische oder verschiedene Veränderungsmechanismen erzielen, wären von besonderer Bedeutung. Eine Übersicht über neuere statistische Methoden im Bereich der Mediationsanalyse wird umfassend von Hayes (2018) und MacKinnon (2017) beschrieben.

Kriterien bei der Bestimmung von Kausalität

Allein der Nachweis einer statistischen Mediation ist nicht ausreichend, um Veränderungsmechanismen zu identifizieren und Kausalität zu bestimmen, d. h., eine Ursache-Wirkung-Beziehung festzustellen. Weitere Kriterien können die Annahme von Veränderungsmechanismen untermauern und die Tragweite von kausalen Inferenzschlüssen erhöhen (Kazdin 2007). Neben den oben genannten Kriterien der *theoretischen Fundierung* eines plausiblen Veränderungsprozesses und der Notwendigkeit eines *starken statistischen Zusammenhangs* (zwischen Intervention, Mediator und Behandlungsergebnis), kommt der zeitlichen Abfolge eine überragende Rolle bei der Annahme von Kausalität zu. Die Grundvoraussetzung der *Zeitlichkeit* (oder „Vorgeordnetheit") ist erfüllt, wenn eine zeitliche Abfolge derart nachgewiesen werden kann, dass die Intervention zunächst zu einer Veränderung im Mediator führt, und dass dieser Änderung im Mediator wiederum zeitlich Veränderungen im therapeutischen Zielbereich/im Behandlungsergebnis (etwa Symptomänderungen) vorausgehen – und nicht andersherum (Kazdin 2007). Deshalb können nur Studien mit einem longitudinalen Versuchsaufbau – mit mehreren gleichzeitigen Erhebungen des Mediators und der Ergebnisvariablen über mindestens 3 Messzeitpunkte hinweg – als geeignet betrachtet werden, um dieses Kriterium zu prüfen und die tatsächliche Richtung und Art der Veränderung zu bestimmen. Die Kriterien *Spezifität* (des Zusammenhangs zwischen der Intervention, dem Mediator und dem Ergebnis), *Gradient* (im Sinne einer Dosis-Wirkung-Beziehung zwischen dem Mediator und dem Ergebnis) und *Konsistenz* (der Ergebnisse zu bestimmten Mediatoren über mehrere Studien hinweg) können die Annahme von Kausalität weiter stützen (Kazdin 2007). Darüber hinaus sind Befunde aus *experimentellen Untersuchungen* von besonderem Wert, um kausale Inferenzschlüsse ziehen zu können. Dies kann entweder durch die Zufallszuweisung einer angemessenen Zahl an Studienteilnehmenden zu verschiedenen Vergleichsgruppen in einem RCT erreicht werden, oder durch die direkte Manipulation einer Mediatorvariable in einem Experiment selbst (Kazdin 2007). Im zuletzt genannten Versuchsaufbau ist eine kausale Schlussfolgerung, dass die experimentelle Manipulation des Mediators (etwa die direkte Induktion von Besserungserwartungen oder positiven Interpretationen durch die therapeutische Ansprache oder digital umgesetztes Priming) die beobachteten Veränderungen im Ergebnis bewirkt, gesichert. Dagegen kann im erst genannten Ansatz lediglich

angenommen werden, dass die Interventionseffekte durch das angenommene Konstrukt mediiert werden, und nicht durch andere, konzeptuell abweichende Proxy-Variablen. Dies ist auch der Grund, warum die simultane Erhebung *multipler Mediatoren* empfohlen werden kann, um widerstreitende Hypothesen über tatsächliche therapeutische Prozesse falsifizieren zu können (Kazdin 2007). Insgesamt sind verschiedene Forschungsstränge erforderlich, die die genannten Kriterien ermessen, der gleichen Forschungsfrage nachgehen, dabei jedoch auf unterschiedliche methodische Ansätze zurückgreifen, um spezifische Veränderungsmechanismen zu bestimmen und hinsichtlich ihrer tatsächlichen Kausalität zu prüfen (Ohlsson und Kendler 2019).

Abschließend muss noch festgehalten werden, dass die Kriterien *Spezifität, Gradient* und *Konsistenz* nicht als absolut angesehen werden können und einige wichtige Ausnahmen berücksichtigt werden müssen. Beispielsweise ist es möglich, dass unterschiedliche Behandlungsmodalitäten, wie etwa KVT oder Pharmakotherapie, durch gemeinsame und/oder unterschiedliche Prozesse wirken, auf der gleichen und/oder einer unterschiedlichen Ebene stattfinden (z. B. Verhaltensaktivierung vs. Veränderungen in der Neurotransmission). Und dabei können diese geteilten (z. B. Modifizierung verzerrter Kognitionen) oder unterschiedlichen Mechanismen simultan und/oder aufeinanderfolgend während der Behandlung auftreten, unabhängig voneinander sein oder sich gegenseitig dynamisch beeinflussen (Hofmann et al. 2020). Deswegen ist es von zentraler Bedeutung, zwischen nichtspezifischen kausalen Prozessen und tatsächlich nichtvorhandener Kausalität zu unterscheiden. Zudem gilt es, denkbare differenzielle Zusammenhänge zwischen Interventionen und Mediatoren einerseits sowie Mediatoren und Behandlungsergebnissen andererseits zu berücksichtigen. Darüber hinaus kann der Zusammenhang eines Mediators mit einem Ergebnis linear sein, aber auch in einer anderen Form des Zusammenhangs (z. B. U- oder S-förmig), die nicht mit einer einfachen Dosis-Wirkung-Beziehung in Einklang zu bringen ist, begründet sein (Hofmann et al. 2020). Diese Beispiele sollen veranschaulichen, dass die Befunde zu den Wirkfaktoren und Veränderungsmechanismen von psychotherapeutischen Interventionen über verschiedene Studien hinweg nicht notwendigerweise konsistent sein müssen, sondern, auch aufgrund der Komplexität der Veränderung von menschlichem Erleben und Verhalten, sogar wesentlich voneinander abweichen können.

Chancen und Grenzen digitaler psychotherapeutischer Interventionen

Internet- und mobile-basierten Interventionen wird das Potenzial beigemessen, die psychotherapeutische Versorgung psychischer Störungen ergänzen und erweitern zu können. Diese Annahme gründet sich v. a. in deren speziellen Eigenschaften und möglichen Vorzügen, etwa in Bezug auf Flexibilität und Anonymität der Durchführung, mögliche Kosteneffektivität und potenziell hohe Reichweite. Damit könnten digitale Interventionen einen bedeutsamen Beitrag zur Erweiterung der psychotherapeutischen Versorgung sowie zur Verringerung der beträchtlichen Unterversorgung psychischer Störungen weltweit leisten. Als mögliche Grenzen und Limitationen digitaler psychotherapeutischer Interventionen werden je nach Störungsbild und Indikation geringere Effektstärken, technische Voraussetzungen an Infrastruktur und Nutzenden sowie insbesondere bei mobile-basierten Interventionen eine mangelnde Evidenzbasierung genannt (Domhardt et al. 2021a). Zusätzlich können für manche Patient*innen digitale Interventionen allein nicht ausreichend sein und daher die Gefahr darstellen, dass intensivere und individuell geeignetere Hilfsangebote erst verspätet oder gar nicht in Anspruch genommen werden (Domhardt et al. 2021a). Darüber hinaus können bei IMI alle Nebenwirkungen und adversen Ereignisse auftreten, wie sie auch bei konventioneller Psychotherapie vor Ort bekannt sind (Domhardt et al. 2021a). Spezielle Risiken von IMI können in einem möglichen Datenmissbrauch oder Datenverlust sowie auch in einer asynchronen Kommunikation zwischen Nutzenden und Therapeut*innen liegen, die v. a. im Rahmen von Krisensituationen eine noch stärkere Umsicht und Sorgfaltspflicht nach sich zieht (Domhardt et al. 2021a).

Evidenzbasiertes Wissen über die spezifischen Wirkungsweisen von begleiteten (mit menschlicher Unterstützung) und unbegleiteten (ohne Unterstützung) IMI für psychische Störungen ist von hoher Relevanz, um die Interventionen derart theoretisch und empirisch fundiert weiterentwickeln zu können und so zu einem wissenschaftlich-begründeten und sicheren Einsatz von IMI in der klinischen Routineversorgung beizutragen. Darüber hinaus eröffnen IMI neue technologische und methodologische Möglichkeiten für die Psychotherapieprozessforschung, die auch dazu herangezogen werden könnten, bei der Bestimmung der Veränderungsmechanismen von klassischer Psychotherapie von Angesicht-zu-Angesicht einen Beitrag zu leisten, und nicht nur bei der Identifikation der therapeutisch-aktiven Bestandteile von IMI selbst Untersuchungsgegenstand zu sein (Domhardt et al. 2021c). So ermöglichen IMI eine höhere Standardisierung psychotherapeutischer Interventionen, um darüber fortwährende Konfundierungen der Psychotherapieprozessforschung – wie etwa der tatsächlichen Präsentation des therapeutischen Inhalts („treatment fidelity") oder verschiedener Therapeut*innenvariablen – konstant halten zu können. Die höhere Standardisierungsmöglichkeit dürfte auch dazu beitragen, einzelne Interventionskomponenten eindeutig und reliabel operationalisieren zu können (Domhardt et al. 2019; Furukawa et al. 2019; Steubl et al. 2019, 2021). Damit könnten digitale Interventionen neue Wege eröffnen, die komplexen Prozesse von Psychotherapie in paradigmatische Fragmente zu zerlegen, um die Wirkfaktoren und Veränderungsmechanismen in innovativen experimentellen Studiendesigns evaluieren zu können (Domhardt et al. 2021c). Zudem sind große Stichprobenfallzahlen, die für die Detektion von kleinen, aber klinisch relevanten Mediationseffekten erforderlich sind, im Rahmen von klinischen Studien mit IMI leichter zu realisieren als in der Vor-Ort-Psychotherapie, da Teilnehmende über die Ferne rekrutiert und Interventionen unabhängig von zeitlichen und räumlichen Einschränkungen durchgeführt werden können. Forschungsbemühungen, die von diesen

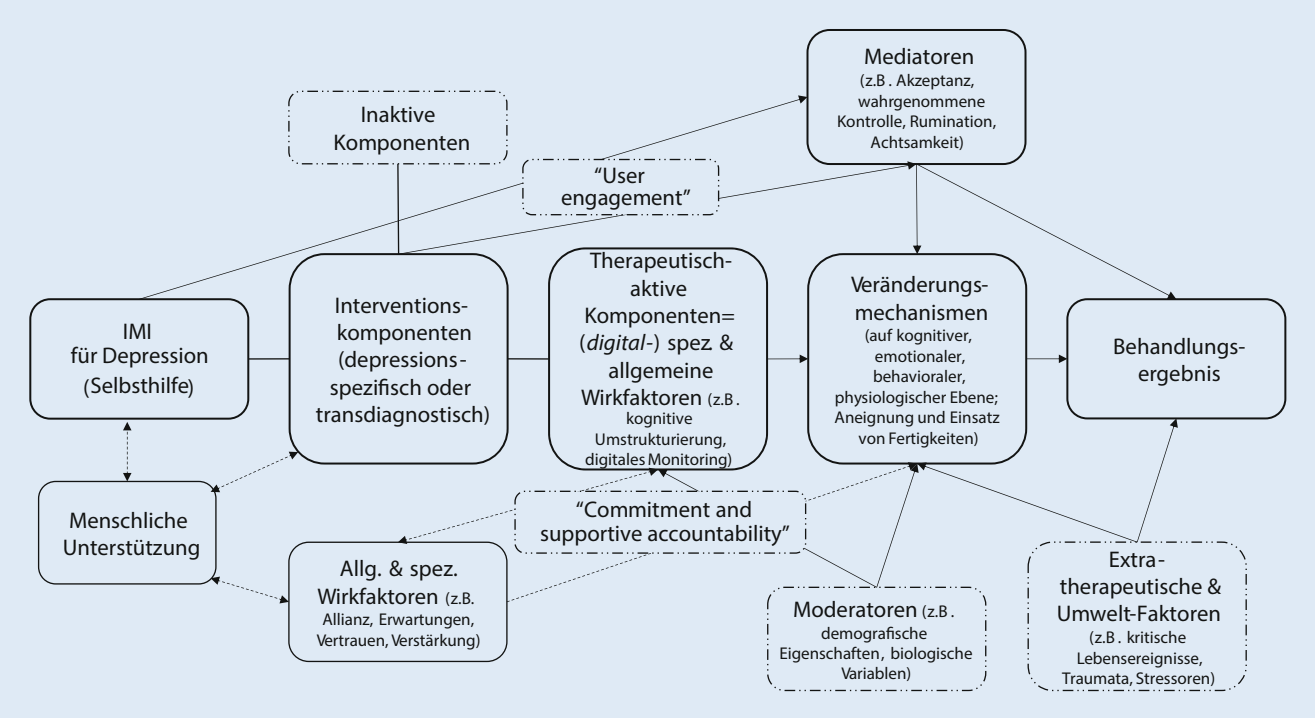


Abb. 1 ▲ Integratives psychologisches Modell der Wirkfaktoren und Veränderungsmechanismen von internet- und „mobile"-basierten Interventionen (*IMI*) für depressive Störungen. Symbole: *Durchgezogene Linien:* bei Interventionen ohne und mit menschlicher Unterstützung („guidance") zutreffend; *gestrichelte Linien:* nur bei Interventionen mit menschlicher Unterstützung (Guidance) zutreffend; *dick umrandete Komponenten:* Kernbestandteile des Modells der Wirkfaktoren und Veränderungsmechanismen; *gestrichelt umrandete Komponenten:* effekt-moderierende Aspekte des Modells bzw. inaktive Komponenten; *Pfeile:* sollen Kausalität (*Pfeil in eine Richtung gehend*) mitsamt zeitlicher Abfolge und auch Bidirektionalität/Wechselwirkung (*Pfeile in beide Richtungen gehend*) und Zeitgleichheit symbolisieren; *Striche* (*ohne Pfeil*): keine Kausalität oder zeitliche Bedeutung. *„User engagement":* Engagement der Nutzenden; *„Commitment and supportive accountability":* Verpflichtung und Hingabe sowie unterstützende Verantwortlichkeit. (Nach Domhardt et al., eingereicht)

Möglichkeiten Gebrauch machen, könnten zu einem besseren Verständnis beitragen, zu welchem Grad technologisch vermittelte und konventionelle Interventionen über geteilte und/oder verschiedene Prozesse ihre Wirkung entfalten; und dabei mit aufklären, ob es tatsächlich spezifische digitale Wirkfaktoren und eigenständige Mediatoren und Veränderungsmechanismen bei IMI für psychische Störungen gibt (Domhardt et al. 2021c).

Wirkungsweisen digitaler Psychotherapie – Vorschlag eines Modells und beispielhafte aktuelle Evidenz zu depressiven Störungen

Das vorgestellte integrative Modell über die möglichen Wirkungsweisen von digitaler Psychotherapie am Beispiel depressiver Störungen greift verschiedene konzeptionelle Überlegungen früherer Modelle auf, die entweder für depressionsspezifische Psychotherapie (Beck und Beck 1972; Beck et al. 1979; Hautzinger et al. 2012; Hautzinger und Bailer 1993; Hautzinger und Meyer 2016; Hollon et al. 1990; Lorenzo-Luaces et al. 2015) oder transdiagnostische psychotherapeutische Interventionen formuliert wurden (Cuijpers et al. 2019b). Zudem wurden bei der Konzeption Einflüsse aus transdiagnostischen Modellen von IMI aufgenommen (Graham et al. 2019; Mohr et al. 2014; Ritterband et al. 2009; Mohr et al. 2011; Yardley et al. 2016). Die finale Fassung des integrativen psychologischen Modells der denkbaren Wirkungsweisen von IMI bei Depressionen ist in ◘ **Abb. 1** dargestellt. Mit den nachfolgenden Ausführungen sollen die einzelnen Bestandteile des Modells vorgestellt, die technologischen Eigenheiten erörtert und die Evidenz zu einzelnen Aspekten des Modells anhand aktueller empirischer Befunde diskutiert werden.

Komponenten internet- und „mobile"-basierter Interventionen zur Therapie von Depression

In dem vorliegenden Modell werden IMI für depressive Störungen entweder als reine Selbsthilfeinterventionen oder als Interventionen mit unterschiedlichen Ausmaßen und Arten der menschlichen Unterstützung („guidance") konzipiert (Baumeister et al. 2014). Dabei bestehen sowohl unbegleitete als auch begleitete Interventionen aus mehreren depressionsspezifischen und/oder transdiagnostischen Interventionskomponenten, die theoretisch fundiert sind und in thematisch kohärenten Modulen umgesetzt werden. Die einzelnen Komponenten können nach ihrer Umsetzung/Durchführung mit unterschiedlicher Intensität therapeutisch-aktiv sein und in Form von spezifischen oder allgemeinen Wirkfaktoren Veränderungsmechanismen in Patient*innen hervorrufen; demgegen-

über ist es auch denkbar, dass einzelne Komponenten inaktiv sind (d. h. nicht therapeutisch wirksam) und überhaupt nicht zu (Symptom)Veränderungen bei Patient*innen beitragen (Hollon et al. 1990; Cuijpers et al. 2019b). Die Konzepte von Komponenten und Wirkfaktoren sind zuallermeist deckungsgleich; die einzelnen Komponenten wurden idealerweise bereits in Studien zu klassischer Psychotherapie von Angesicht zu Angesicht evaluiert und können somit als evidenzbasierte „konventionelle" Wirkfaktoren betrachtet werden. Dahingegen könnten manche Interventionskomponenten vollkommen neuartig sein und aufgrund ihrer technologischen Umsetzung ausschließlich in digitaler Psychotherapie zum Tragen kommen und damit eine neue Kategorie der *digitalen Wirkfaktoren* bilden (Domhardt et al. 2021b). Diese neu postulierten digitalen Wirkfaktoren könnten analog zu konventionellen Wirkfaktoren in *digital-allgemeine* und *digital-spezifische* Wirkfaktoren unterteilt werden. Digital-allgemeine Wirkfaktoren wären demnach allen technologisch-vermittelten Interventionen immanent, wie etwa die technologische Vermittlung der Interventionsinhalte oder technologische Design-Aspekte. Digital-spezifische Wirkfaktoren wären dahingegen eigens für bestimmte digitale Gesundheitsinterventionen charakteristisch, wie z. B. „Persuasive-design"-optimierte Interventionen (Baumeister et al. 2020), personalisiertes und automatisiertes Feedback oder digitales Monitoring von Bewegungen. Im Gegensatz zu den umfangreichen konzeptuellen Überlegungen zu den allgemeinen und spezifischen Wirkfaktoren in klassischen Psychotherapien mit verschiedenen theoretischen Hintergründen (Mulder et al. 2017; Pfammatter und Tschacher 2016) muss das Konzept der digitalen Wirkfaktoren erst noch umfassend geprüft und weiterentwickelt werden.

Aktuelle Erkenntnisse zu den therapeutisch-aktiven Interventionskomponenten internetbasierter KVT (iCBT) konnten in einer jüngst publizierten Netzwerkmeta-analyse erzielt werden (Furukawa et al. 2021). Mit dieser neuartigen Netzwerkmethode, die auf individuelle Teilnehmerdaten („individual participant data", IPD) zurückgreift, werden Interventionskomponenten über Studien hinweg mit hoher statistischer Teststärke verglichen, wodurch Wissen generiert werden kann, das im Rahmen von einzelnen RCT- und Komponentenstudien bisher nicht zu ermitteln war (Furukawa et al. 2019). Die zentralen Ergebnisse dieser Studie deuten darauf hin, dass offenbar die Interventionskomponente Verhaltensaktivierung („behavioral activation") sowie unspezifische Behandlungseffekte wie Placeboeffekte und allgemeine Wirkfaktoren entscheidend zur Wirksamkeit von iCBT beitragen, wohingegen Entspannungstechniken („relaxation") für die Wirksamkeit abträglich zu sein scheinen (Furukawa et al. 2021).

Mediatoren und Veränderungsmechanismen

Es ist zu vermuten, dass spezifische und allgemeine Wirkfaktoren unterschiedliche Mediatoren und Veränderungsmechanismen auf verschiedenen Ablaufebenen (etwa von Molekülen, Zellen und neuronalen Kreisläufen, hin zu Kognitionen, Emotionen und Verhaltensweisen) induzieren, unabhängig davon, ob sie konventionellen oder digitalen Wirkfaktoren zuzurechnen sind. Die angestoßenen Veränderungsmechanismen in Patient*innen können gleichzeitig oder nacheinander folgend auf kognitiver, verhaltensbezogener, emotional/affektiver und/oder biologisch/physiologischer Ebene ablaufen. Außerdem können diese Prozesse eigenständig erfolgen oder sich gegenseitig beeinflussen und aufgrund von Wechselwirkungen zu intensivierten oder abgeschwächten Veränderungsmechanismen und daraus resultierenden Behandlungsergebnissen führen. Mediatoren können, wie weiter oben beschrieben, entweder mit tatsächlichen Veränderungsmechanismen übereinstimmen oder aber lediglich Proxy-Variablen für andere Konstrukte darstellen (Kazdin 2007; Cuijpers et al. 2019b). Dementsprechend werden die Mediatoren und Veränderungsmechanismen im vorliegenden Modell über verschiedene Pfade repräsentiert, auch wenn sie in manchen Fällen übereinstimmen und identisch sein können.

In einem systematischen Review der Autoren erfolgte eine erste umfassende Übersicht über empirisch fundierte Mediatoren von IMI für Depression (Domhardt et al. 2021b). Die Befunde stützen die Annahme, dass die bislang untersuchten Mediatoren von IMI eine hohe Vergleichbarkeit zu den intervenierenden Variablen von konventionellen Psychotherapien für depressive Störungen aufweisen (z. B. Lemmens et al. 2016). Derzeit können jedoch aufgrund methodischer Einschränkungen innerhalb der Mediationsstudien (insbesondere die Kriterien Zeitlichkeit/Vorgeordnetheit und direkte experimentelle Manipulation der Mediatoren betreffend) noch weitgehend keine kausalen Inferenzschlüsse über Veränderungsmechanismen gezogen werden. Im Zentrum des Modells zu den denkbaren Wirkungsweisen digitaler Psychotherapie von Depression sind exemplarisch verschiedene empirische gestützte Mediatoren und Veränderungsmechanismen zur Veranschaulichung aufgeführt (**Abb. 1**).

Engagement

Analog zu anderen psychotherapeutischen Behandlungen wird angenommen, dass das Ausmaß, in dem die Patient*innen die Intervention absolvieren und die (präskriptiven) Therapieinhalte und (Verhaltensänderungs-)Techniken befolgen, zentral ist, um Veränderungsmechanismen zu induzieren und die Intervention wirksam werden zu lassen. Angesichts der besonderen Art von technologiebasierten Interventionen wird jedoch davon ausgegangen, dass das Nutzer*innenengagement bei IMI im Vergleich zu Face-to-face-Psychotherapien von noch größerer Bedeutung ist – ganz besonders bei reinen Selbsthilfeinterventionen, die ohne irgendeine Form von begleitender menschlicher Unterstützung zum Einsatz kommen. In der Literatur zu digitalen Gesundheitsinterventionen finden sich verschiedene Konzeptualisierungen von Engagement (Graham et al. 2019; Yardley et al. 2016; Mohr et al. 2014; Ritterband et al. 2009), die sich entweder auf eine Mikroebene (d. h. unmittelbares/momentanes Engagement mit der digitalen Technologie; Yardley et al. 2016) oder auf eine Makroebene (d. h. Einsatz von Techniken der Verhaltensänderung und Auswirkung von Mediatoren und Veränderungsmechanismen im alltäglichen

Leben; Yardley et al. 2016) beziehen. In dem vorliegenden Modell soll Engagement in Übereinstimmung mit Graham et al. (2019) als Ausmaß definiert werden, zu dem Patient*innen mit der IMI interagieren (Mikroaspekt) und die Therapieinhalte umsetzen (Makroaspekt). Der Mikroaspekt von Engagement kann mithilfe objektiver Nutzungsdaten operationalisiert werden (z. B. bearbeitete Module, eingeloggte Zeit; Yardley et al. 2016; Graham et al. 2019). Forschungsbemühungen, die danach streben, Erkenntnisse zu effektiven Ansätzen zur Steigerung der Nutzungs- und Adhärenzraten und damit mittelbaren Optimierung von Behandlungsergebnissen zu generieren („effektives Engagement"; Yardley et al. 2016), können auf Erkenntnisse aus verschiedenen Disziplinen aufbauen, wie z. B. Mensch-Computer-Interaktion, persuasives Systemdesign, soziales Marketing sowie Kommunikationstechnologie und Webdesign (Yardley et al. 2016; Mohr et al. 2014; Ritterband et al. 2009; Baumeister et al. 2020). Demgegenüber werden die spezifischen und inhaltsbezogenen Mediatoren und eigentlichen Veränderungsmechanismen (Makroaspekt) im Wesentlichen durch die Psychotherapieprozessforschung erzielt.

Die aktuell vorliegende Evidenz untermauert die Annahme einer herausragenden Rolle des Nutzer*innenengagements für stärkere Interventionseffekte von IMI bei Depressionen, besonders bei unbegleiteten Interventionen. So weisen die Ergebnisse einer IPD-Metaanalyse darauf hin, dass der Effekt von selbstangeleiteten IMI bei Patient*innen mit depressiven Störungen, die mehr Module abschließen, höher ausfällt als für diejenigen Patient*innen, die weniger Module absolvieren (Karyotaki et al. 2017). Weiterhin weisen andere empirische Befunde darauf hin, dass die Raten der Patient*innen, die eine Behandlung abschließen, sich nicht signifikant zwischen begleiteten iCBT und konventionellen KVT-Interventionen von Angesicht zu Angesicht unterscheiden (van Ballegooijen et al. 2014). Dessen ungeachtet stellen die vergleichsweisen hohen Drop-out-Raten bei IMI ein großes Problem dar, sodass sich zukünftige Forschung der Frage widmen sollte, wie „effektives Engagement" am besten erreicht werden kann, um die Adhärenzraten von IMI zu erhöhen und die Behandlungsergebnisse insgesamt optimieren zu können (Baumel et al. 2019; Baumel und Kane 2018; Baumel und Yom-Tov 2018).

Therapeutische Begleitung (Guidance) und „supportive accountability"

Bei begleiteten Interventionen kommt ein weiterer Pfad in dem Modell zur Geltung, der der besonderen Bedeutung von menschlicher Unterstützung im Rahmen von IMI Rechnung tragen soll (Baumeister et al. 2014). Die therapeutische Begleitung könnte ihre Wirksamkeitsvorteile mithilfe konventioneller allgemeiner und spezifischer Wirkfaktoren erzielen, die aus konventionellen Psychotherapien vor Ort bekannt sind und mit der therapeutischen Allianz in Verbindung stehen. Dementsprechend könnte eine technologisch vermittelte therapeutische Beziehung (Steinhoff et al. 2020) bei IMI für Depressionen analog zu klassischen psychotherapeutischen Interventionen eine tragende Rolle spielen. Diese digitale therapeutische Allianz löst möglicherweise Prozesse aus, die in reinen Selbsthilfeinterventionen nicht induziert werden (Steinhoff et al. 2020). Dabei könnten die mit der menschlichen Unterstützung zusammenhängenden Wirkfaktoren und Mediatoren einerseits direkt Veränderungsmechanismen in den Patient*innen auslösen oder andererseits mit weiteren (digitalen) Komponenten in Wechselwirkung treten (Domhardt et al. 2021b), was durch einen bidirektionalen Pfeil dargestellt werden soll. Grundsätzlich ist es möglich, dass sog. e-Coaches (d. h. speziell geschulte Fachkräfte, die die Unterstützung innerhalb der Intervention anbieten) bestimmte Komponenten der IMI an die Bedürfnisse/Erfordernisse der Patient*innen anpassen („tailoring"), und Patient*innen, die nicht auf die digitale Intervention ansprechen, einer intensiveren Behandlung im Rahmen eines gestuften Versorgungsmodells („stepped care") zuweisen kann (Domhardt und Baumeister 2018).

Die therapeutische Begleitung und die damit im Zusammenhang stehende (digitale) Therapiebeziehung könnten das Commitment von Patient*innen einerseits zur als e-Coach fungierenden Fachkraft und der Intervention selbst und auch andererseits zu den eigenen Zielen für die angestrebte Verhaltensänderung erhöhen. Weiterhin nehmen Mohr et al. (2011) an, dass die größeren Effektstärken von begleiteten IMI hauptsächlich durch die Verantwortlichkeit gegenüber dem e-Coach („supportive accountability"), der als vertrauenswürdig, unterstützend, kompetent und legitimiert angesehen wird, zurückzuführen sind.

Es ist empirisch gut belegt, dass IMI mit begleitender Unterstützung in der Behandlung von Symptomen psychischer Störungen signifikant wirksamer sind als selbstgeleitete Interventionen (Baumeister et al. 2014; Domhardt et al. 2019), und dass die therapeutische Beziehung ebenso mit den Ergebnissen internetbasierter Interventionen zusammenhängt, wie dies bereits von konventioneller Psychotherapie bekannt ist (Flückiger et al. 2018). Diese Befunde gelten auch in hohem Maß für den Bereich Depression, in dem begleitende menschliche Unterstützung in digitalen Interventionen konsistent zu höheren Adhärenzraten und besseren Behandlungsergebnissen im Vergleich zu reinen Selbsthilfeinterventionen führt, so auch in der aktuell veröffentlichen IPD-Netzwerk-Metaanalyse zur iCBT (Furukawa et al. 2021). Darüber hinaus weisen aktuelle metaanalytische Befunde zu direkten Vergleichen zwischen begleiteten IMI und konventionellen Psychotherapien darauf hin, dass diese unterschiedlichen Darbietungsmodalitäten und Interventionstypen in der Behandlung depressiver Symptome vergleichbare Effekte aufweisen (Carlbring et al. 2018). Ungeachtet dieses als vorläufig einzuordnenden Befundes sollten zukünftige Studien darauf abzielen, offene Forschungsfragen im Hinblick auf mögliche Dosis-Wirkung-Zusammenhänge zwischen therapeutischer Begleitung und Behandlungsergebnissen, dem benötigten Ausmaß an Unterstützung und dem Qualifikationsniveau von e-Coaches (Baumeister et al. 2014) sowie Stärken und Limitationen von automatisierten Formen von Unterstützung (Domhardt et al. 2019; Mohr et al. 2014; Ritterband et al. 2009) zu klären.

Selbsthilfeinterventionen

Im Fall von reinen Selbsthilfeinterventionen ist der untere Pfad, der mit der menschlichen Unterstützung in Verbindung steht, nicht zutreffend (was in Form einer gestrichelten Linie in **Abb. 1** zum Ausdruck gebracht werden soll). Im Unterschied zu begleiteten Interventionen könnte das von den Patient*innen in unbegleiteten IMI verstärkt erforderliche Selbstmanagement die Mediatoren wahrgenommene Kontrolle und Selbstwirksamkeit in einem höherem Ausmaße anregen. Nichtsdestotrotz müssen diese vorläufigen Ergebnisse durch weitere empirische Untersuchungen untermauert werden; mitsamt Studien darüber, wie die bislang zu findenden substanziellen Dropout-Raten in selbstgeleiteten IMI – die in „real-world settings" noch ausgeprägter zu sein scheinen (Baumel et al. 2019) – am effektivsten reduziert werden können.

Moderatoren

Moderatoren und andere außertherapeutische Faktoren sowie Umweltfaktoren können auf die Veränderungsmechanismen selbst (moderierte Mediation) Einfluss nehmen und mit ihnen interagieren und darüber das Therapieergebnis mittelbar beeinflussen; stellen jedoch selbst keine Veränderungsmechanismen dar. Moderatoren können vielmehr auf mögliche unterschiedliche Mechanismen in bestimmten Subgruppen hinweisen (Kazdin 2007). Effektmodifizierende Faktoren werden in diesem Modell mithilfe von Kästen mit gestrichelten dünnen Linien dargestellt, um sie von den Kernprozessen und eigentlichen Veränderungsmechanismen (in Kästen mit durchgezogenen und fett hervorgehobenen Linien) abzugrenzen. Detailliertes evidenzbasiertes Wissen über Moderatoren und Prädiktoren würde enorm zur Personalisierung von Psychotherapie beitragen können, Zuweisungsentscheidungen vor einer Behandlung fundieren und sicherstellen, dass einzelne Patient*innen die für sie am besten geeignete und effektivste Intervention erhalten (Cohen und DeRubeis 2018).

Mögliche ätiologische, moderierende und prädiktive Variablen (wie z. B. Alter, Geschlecht, genetische Prädisposition, biologischer Stress, frühe Lebensereignisse, Komorbidität oder Symptomschweregrad) wurden in der konventionellen Psychotherapieforschung depressiver Störungen bereits umfassend untersucht. Mit hoher Wahrscheinlichkeit spielen einige dieser Variablen ebenfalls eine wichtige effektmoderierende Rolle bei technologisch-vermittelten Interventionen. Spezifisches Wissen über die Moderatoren und Prädiktoren von IMI ist unabdingbar für die Bestrebungen zur Personalisierung von Psychotherapie und digitaler Gesundheitsinterventionen. Bislang konnte eine aktuelle IPD-Metaanalyse zeigen, dass höheres Alter, Ethnie (gebürtig im Land der Studie) und höherer Ausgangsschweregrad der depressiven Symptomatik das Ansprechen auf die Behandlung („Response") und die Remission bei begleiteten IMI für Depression moderierten (Karyotaki et al. 2018); wohingegen eine andere IPD-Metaanalyse keine Moderatoren oder Prädiktoren für unbegleitete iCBT-Interventionen nachweisen konnte (Karyotaki et al. 2017). Weiterhin ergab eine aktuelle IPD-Metaanalyse über Moderatoren von internetbasierten Interventionen für subklinische Depression, dass ein hoher Ausgangsschweregrad der depressiven Symptomatik, das Vorliegen von chronischen Erkrankungen und menschliche Unterstützung mit stärkeren Effekten einhergehen (Reins et al. 2020).

Von der theoretischen Konzeptualisierung hin zur empirischen Fundierung

Abschließend sollen noch einige Gedanken geäußert werden, um das vorgestellte Modell zu rahmen, den angedachten Zweck zu bezeichnen und seine aktuelle empirische Grundlage einzuordnen. Die primäre Intention der Modellentwicklung bestand darin, die empirische Forschung zu Veränderungsmechanismen von IMI konzeptuell anzuleiten, da zentrale Konstrukte der Psychotherapie(prozess)forschung in der Literatur häufig missverständlich, willkürlich oder beliebig eingesetzt werden. Dies gilt z. B. für die Konzepte der Mediatoren vs. Moderatoren oder Komponenten und Wirkfaktoren (die Teil der Intervention sind) auf der einen Seite vs. Mediatoren und Veränderungsmechanismen (die bei Patient*innen auftreten) auf der anderen Seite (Cuijpers et al. 2019b). Eine klare Unterscheidung und A-priori-Operationalisierung dieser Konstrukte kann dazu beitragen, die empirische Bestimmung ihrer Rollen als einzelne Entitäten, aber auch ihrer Zusammenhänge und Wechselwirkungen in zukünftiger Forschung zu befördern und damit zu stärkeren kausalen Schlussfolgerungsmöglichkeiten beitragen. Dabei soll das vorgeschlagene Modell nicht notwendigerweise auf die Wirkungsweisen digitaler Interventionen der Depressionsbehandlung beschränkt sein; es ist ebenso denkbar, dass es auf andere häufige psychische Störungen angewendet werden kann und lediglich die entsprechenden inhaltsbezogenen Teile adaptiert werden müssten.

Aktuell sind die Richtungen der Pfeile in diesem Modell, die repräsentativ für die Zuweisung von Ursache und Wirkung stehen sollen, vorwiegend konzeptioneller Natur und noch nicht ausreichend empirisch gestützt. Daher ist es ebenfalls denkbar, dass die Richtungen der Kausalketten in manchen Fällen gegensätzlich (d. h. umgekehrte Kausalität), zirkulär oder bidirektional ausfallen – oder sogar überhaupt nicht existent sind.

Fazit

- **Aufgabe zukünftiger Forschung sollte es sein, die kausalen Beziehungen, die im oben beschriebenen Modell über die möglichen Wirkungsweisen von digitaler Psychotherapie am Beispiel depressiver Störungen vorgeschlagen wurden, empirisch zu validieren oder zu falsifizieren.**
- **Dabei ist zu berücksichtigen, dass die Prozesse in psychotherapeutischen Interventionen von enormer Komplexität sind, und dass die in diesem Modell skizzierten Vorstellungen notwendigerweise eine Vereinfachung des Gegenstandsbereichs darstellen müssen.**
- **Das vorgestellte integrative psychologische Modell könnte von Nutzen sein, um die Komplexität psychotherapeutischer Veränderungsprozesse zu reduzieren, und ein paradigmatisches Rahmenkonzept für zukünftige Studien zu bieten, um die Wirkungsweisen digitaler psychotherapeutischer Interventionen zu identifizieren.**

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Einhaltung ethischer Richtlinien

Interessenkonflikt. M. Domhardt und H. Baumeister geben an, dass kein Interessenkonflikt besteht.

Für diesen Beitrag wurden von den Autoren keine Studien an Menschen oder Tieren durchgeführt. Für die aufgeführten Studien gelten die jeweils dort angegebenen ethischen Richtlinien.

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Abstract

Active ingredients and mechanisms of change in digital psychotherapy

Although the efficacy and effectiveness of internet-based and mobile-based interventions for various mental disorders can now be considered to be well established, robust knowledge about the specific mechanisms of change in digital psychotherapy is scarce. This article first describes the key concepts and methods of psychotherapy process research (e.g., common and specific factors, component studies, mediators and mechanisms of change) and based on this an integrative psychological model of the potential mechanisms of action in digital psychotherapy is presented. The individual components of this model are discussed based on the empirical evidence, for example in depressive disorders, with a perspective with respect to central research desiderata.

Keywords
Internet · Mobile health · Digital health intervention · Mechanism of change · Psychotherapeutic processes

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Part III

Possibilities and challenges of digitalized approaches in psychotherapy process research

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Chapter 6

More light? Opportunities and pitfalls in digitalised psychotherapy process research

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More Light? Opportunities and Pitfalls in Digitalized Psychotherapy Process Research

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While the evidence on the effectiveness of different psychotherapies is often strong, it is not settled *whereby* and *how* these therapies work. Knowledge on the causal factors and change mechanisms is of high clinical and public relevance, as it contributes to the empirically informed advancement of psychotherapeutic interventions. Here, digitalized research approaches might possess the potential to generate new insights into human behavior change, contributing to augmented interventions and mental healthcare practices with better treatment outcomes. In this perspective article, we describe recent findings of research into change mechanisms that were only feasible with digital tools and outline important future directions for this rather novel branch of research. Furthermore, we indicate several challenges and pitfalls that are to be solved, in order to advance digitalized psychotherapy process research, both methodologically and technologically.

Keywords: psychotherapy, mechanisms of change, e- and m-health, mediators, components, active ingredients, digital factors

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INTRODUCTION

Despite decades of research efforts to unveil the working mechanisms in psychotherapies for common mental disorders, the evidence base on the causal factors and therapeutic processes in most of these interventions remains largely uncertain (Cuijpers et al., 2019). Most researchers would probably agree that comprehensive knowledge on the mechanisms of change (i.e., the actual processes responsible for change) is central to develop more powerful intervention packages with optimized outcomes though. We highlight that certain features of digitalization convey novel opportunities for psychotherapy process research, which hold the potential to lift this kind of research on another level and shed *more light* upon an enduring *black box*. At the same time, we also point to important challenges and hurdles that might obstruct the full evolvement of this new branch of research.

Here, we conceive *digitalized* psychotherapy process research rather broadly, comprising different methods and means, which share the commonality that they are all technologically realized and were not available to prior psychotherapy research of the pre-digital age. Established examples of these digital approaches are video-taped analyses of therapeutic processes (e.g., Koole and Tschacher, 2016), videoconference-based psychotherapy (e.g., Etzelmueller et al., 2018), or routine outcome monitoring (e.g., Lutz, 2002; Lambert et al., 2018). These digital tools might be predominantly applied for research purposes only, but might also directly

support psychotherapeutic practices in clinical routine. Most prominently, eHealth and mHealth interventions (i.e., psychotherapeutic treatment programs that are either delivered via personal computers and web-browsers, or smartphones and mobile applications, respectively) are extensively researched in recent years and show promise to extend mental healthcare, given their particular features, like flexibility and anonymity in conduct, possible cost-effectiveness, and outreach on a population scale (Andersson et al., 2019; Linardon et al., 2019; Domhardt et al., 2020a). Moreover, internet- and mobile-based interventions (IMIs) might not only augment the capabilities in mental healthcare (Ebert et al., 2017) but also hold a considerable potential for psychotherapy research on change mechanisms because of their specific properties.

NOVEL METHODOLOGICAL AND TECHNOLOGICAL OPPORTUNITIES

To begin with, a major asset of the implementation of IMIs in psychotherapy process research is the possibility to reach a higher standardization of interventions and their components, which was not possible with previous conventional research approaches within face-to-face therapy settings. This methodological progression enables a more reliable detection of the effects of single components in dismantling and additive design studies (Steubl et al., 2019), as previously hard to control confounds, like therapist factors (e.g., personal views, professional experience, and skills) or the actual presentation of manualized therapeutic content, can be hold constant. Thereby, dismantling studies have revealed several important insights so far, for example, the superiority of IMIs with guidance compared to pure self-help interventions (Baumeister et al., 2014) or the comparable effectiveness of transdiagnostic and disorder-specific interventions (Domhardt et al., 2019). These preliminary findings suggest that the therapeutic alliance might play a prominent role as common factor in digitalized psychotherapeutic interventions as well (Berger, 2016), and the potential of IMIs for scalability purposes might be further amplified by means of transdiagnostic treatment manuals (e.g., Weisel et al., 2019). Yet, future studies must expand our knowledge by disentangling the incremental or surrogating effects of central other components, like automation of support (as a possible cost-efficient alternative of human support in IMIs) and tailoring of intervention content to patients' needs (in contrast to "one-size-fits-all"-interventions), in order to fully grasp the actual potential and limitations of IMIs to extend and augment mental healthcare efforts on a global scale.

Another advantage of experimental studies with IMIs is that they enable an unprecedented way to break down the utterly complex and dynamic processes of psychotherapeutic interventions into paradigmatic fragments, with the direct manipulation of isolated and clearly operationalized specific factors. In this sense, digital interventions might serve as a "mouse model" for psychotherapy process research and allow for the evaluation of distinct psychological and biological mechanisms of therapeutic change in original experimental designs. For instance, Hirsch et al. (2018) investigated the effects of experimentally inducing positive interpretations by means of a priming task before internet-delivered cognitive bias modification training (CBM) in patients with symptoms of depression and anxiety. The authors found that changes in interpretation bias partially mediated the effects of CBM on worry and rumination at follow-up, contributing to our understanding of the causal role of interpretation bias in worry and rumination, as a relevant target for face-to-face and online psychotherapy alike (Hirsch et al., 2018).

Moreover, ecological momentary assessment (EMA) and smart sensing studies make the step out of laboratories and facilitate the immediate detection of variables, irrespective of the constraints of space and time (Myin-Germeys et al., 2018). This can eventually lead to more valid multimodal assessments (i.e., "digital phenotyping"; Jain et al., 2015; Baumeister and Montag, 2019), free from several biases (e.g., recall, social desirability; Shiffman et al., 2008) and without overlapping measurements of outcome and mediator constructs in ordinary paper–pencil self-reports with similar—or even identical—items. Future research is needed however, to investigate, if novel biases arise within EMA studies themselves (e.g., reactive assessment; van Ballegooijen et al., 2016). The ease and high-intensity of data collection with EMA (Schuster et al., 2020) and digital tools will ultimately lead to larger sample sizes and big data sets that would alleviate the problem of limited statistical power, which is a long-lasting impediment of psychotherapy (process) research (Domhardt et al., 2021). This assumption is corroborated in a recent review, showing that mediation studies with IMIs for depression (Domhardt et al., 2021) exhibit a substantial larger amount of study participants on average (M = 262, SD = 243), when compared to conventional psychotherapy process research for depression (Lemmens et al., 2016; M = 173, SD = 145).

Fine-grained longitudinal data on therapeutic processes, gathered within or outside therapy sessions, can be shared among researchers conducting individual patient data meta-analyses, in order to develop multivariable algorithms that contribute to precision mental health (Furukawa et al., 2018, 2019; Lin et al., 2019). Innovative machine learning approaches might predict trajectories of change based on these data, which can inform pre-treatment and in-session decisions of mental healthcare practices (Cohen and DeRubeis, 2018; Goldberg et al., 2020; Rubel et al., 2020). Additionally, virtual reality (VR) interventions reveal novel findings on change mechanisms that were not conceivable with conventional studies so far. For instance, in their original study Pot-Kolder and colleagues randomized 116 patients with psychotic disorders either to VR-based Cognitive Behavior Therapy (CBT) or waitlist (treatment as usual). The VR-CBT intervention consisted of 16 sessions (8–12 weeks) with therapist-guided virtual-reality exercises, comprising reflections and challenges about the patients' suspicious thoughts, safety behaviors, and harm expectancies. At this, the virtual social environments were individually designed for each patient, matching the idiosyncratic cues and paranoid fears of the individual patient. It goes without saying that the variations in the number, characteristics and responses of human avatars in VR would have not been controllable in real life exposure

sessions. Overall, the findings of this recent RCT indicate that safety behaviors and modified social cognitions were mediators of treatment change and contributed to reductions in momentary paranoid ideation and anxiety (Pot-Kolder et al., 2018).

CURRENT CHALLENGES AND IMPLICATIONS FOR FUTURE RESEARCH

However, to exploit the full potential of digitalized approaches to psychotherapy process research, it is essential to address several prevailing pitfalls and ethical considerations. These are, amongst others, fundamental data security, confidentiality, and emergency issues, as well as concerns in regard to certain unresolved research questions (Stoll et al., 2019). For example, a major confinement in IMIs is a comparatively high attrition rate and limited engagement of patients in these digital interventions, especially when they are unguided and transferred from controlled research settings into routine healthcare (Domhardt et al., 2019; Graham et al., 2019). Numerous research efforts are currently committed to find effective ways to increase the engagement—i.e., the frequency patients adopt and interact with IMIs (Graham et al., 2019)—such as user-centered design (Graham et al., 2019), product quality and therapeutic persuasiveness (Baumel and Kane, 2018), striving for higher completer rates and, as a consequence thereof, better treatment outcomes (Yardley et al., 2016). Likewise, several attempts and efforts are currently underway, in order to reach a better understanding of the attitudes of patients, therapists and stakeholders toward IMIs (Topooco et al., 2017; Apolinário-Hagen et al., 2018), as well as to establish legal and regulatory frameworks for the implementation of IMIs (Ebert et al., 2018), in order to pave the way for a broader dissemination of digital psychotherapeutic interventions in research and practice.

Aside these current challenges, there are conceptual and methodological confines that hampered the field of psychotherapy process research for decades. This holds true for divergent operationalizations of central constructs of psychotherapy research, which ancillary obstructed the long-lasting debate about the relative importance of common and specific factors (Mulder et al., 2017). For instance between "factors" and "components" that are part of the therapy (e.g., problem solving training), versus "mediators" and "mechanisms of change" that occur in the patient (e.g., application of newly acquired problem solving skills). Other examples of somewhat tenacious misconceptions in the literature are between "moderators" and "mediators" (Johansson and Høglend, 2007). Thus, next to the importance to stick to consistent operationalizations of existing constructs, it is also key to conceptualize certain unique features of digital interventions that might represent novel *digital common* or *digital specific factors*. Therewith we refer to factors that are *common* to all (e.g., technological design and delivery) or *specific* to certain digital health interventions (e.g., persuasive design, mobile sensing and ecological momentary interventions, and continuous automated feedback with smartphones or wearables)—but are not constituent of face-to-face psychotherapies. Future research must disclose, which of these digital factors are indeed active ingredients of technology-delivered interventions (or are merely facilitating or obstructive moderating variables for genuine therapeutic processes), and if they induce the same or separate working mechanisms when compared to conventional face-to-face psychotherapies. Albeit, these questions of comparative research are hardly to answer, as long as there are substantial differences between these two branches of research concerning recruitment strategies and sample characteristics (Torous and Firth, 2018). Another current confinement of digital approaches to psychotherapy research is their primary focus on interventions based on CBT-principles to this point (Andersson et al., 2019; Domhardt et al., 2020b). Hence, IMIs developed from other therapeutic backgrounds (such as psychodynamic, interpersonal or mindfulness-based approaches) are of value to expand the evidence base—therewith omitting an imbalance still observable in conventional psychotherapy research today (Leichsenring et al., 2018).

An additional major current concern lies in the light-minded interchange of correlation and causality with flawed conclusions on presumed psychological processes (Antes, 2016; Caliebe et al., 2019), as observed in some privately funded studies resorting to big data gathered by large tech companies. Hence, it is of utmost importance to comply with the traditional explanatory research sequence: hypothesize, model, and test (Anderson, 2008). Alongside the cautious contemplation of central notions of epistemology (i.e., verify vs. falsify; Carnap, 1928; Popper, 1959) and approaches to causal inference (Ohlsson and Kendler, 2019). Thereby, an attentive awareness of the differences between conventional and digitalized research methods in deriving knowledge from big data is of high relevance, as certain automated approaches lack testable hypotheses, conceptual frameworks or theoretical foundations (Kriston, 2020), as indispensable theoretical presuppositions for causal inferences (Wilkinson et al., 2020). As such, some methods relying on machine learning and artificial intelligence are not suitable to detect causal mechanisms in clinical settings, as they might impede transparency and replicability, which have to remain indispensable criteria for various decisions in healthcare. Hence, the consideration and advocacy of theory-driven explanatory research with falsifiable scientific models might be of particular relevance at the present time, so as to convey the scientific achievements and epistemological methodologies from decades of research efforts into an ever-increasing digitalized world, with the concomitant advancement of technologized psychological and medical research.

CONCLUSION

Last but not least, in our view, the discussion about the opportunities and limitations of digitalized approaches to psychotherapy process research must not attend to technological

and methodological aspects alone, but urgently needs to weigh the clinical and societal implications of their (non-)utilization hereafter. Accordingly, forthcoming research efforts ought to reveal, to which degree the innovations of digitalization will actually add *more light* on the mechanisms of change in psychotherapeutic interventions, and if we make the most out of technological opportunities to improve global mental health.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding author/s.

AUTHOR CONTRIBUTIONS

MD wrote the first draft of the manuscript. All authors have contributed to the further writing and have approved the final manuscript.

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Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Part IV

Specific and common factors as active ingredients of digital interventions

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Chapter 7. * Domhardt, M., Geßlein, H., von Rezori, R., & Baumeister, H. (2019). Internet- and mobile-based interventions for anxiety disorders: A meta-analytic review of intervention components. *Depression and Anxiety, 36*, 213-224. https://doi.org/10.1002/da.22860

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Chapter 7

Internet- and mobile-based interventions for anxiety disorders: A meta-analytic review of intervention components

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REVIEW

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Internet- and mobile-based interventions for anxiety disorders: A meta-analytic review of intervention components

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[Correction added on November 30, 2018, after first online publication: figure 2 was replaced with correct version.]

Background: Although the efficacy of Internet- and mobile-based interventions (IMIs) for anxiety is established, little is known about the intervention components responsible for therapeutic change. We conducted the first comprehensive meta-analytic review of intervention components of IMIs for adult anxiety disorders.

Methods: Randomized controlled trials (RCTs) comparing IMIs for anxiety disorders to active online control groups, or IMIs to dismantled variations of the same intervention (± specific components) were identified by a systematic literature search in six databases. Outcomes were validated observer-rated or self-report measures for anxiety symptom severity and treatment adherence (number of completed modules and completer rate). This meta-analytic review is registered with PROSPERO (CRD42017068268).

Results: We extracted the data of 34 RCTs (with 3,724 participants) and rated the risk of bias independently by two reviewers. Random-effects meta-analyses were performed on 19 comparisons of intervention components (i.a., different psychotherapeutic orientations, disorder-specific vs. transdiagnostic approaches, guidance factors). IMIs had a large effect when compared to active online controls on symptom severity (standardized mean difference [*SMD*] of −1.67 [95% CI: −2.93, −0.42]; $P = 0.009$). Thereby, guided IMIs were superior to unguided interventions on symptom severity (*SMD* of −0.39 [95% CI: −0.59, −0.18]; $P = 0.0002$) and adherence (*SMD* of 0.38 [95% CI: 0.10, 0.66]; $P = 0.007$).

Conclusions: Overall, the results of this meta-analysis lend further support to the efficacy of IMIs for anxiety, pointing to their potential to augment service supplies. Still, future research is needed to determine which ingredients are essential, as this meta-analytic review found no evidence for incremental effects of several single intervention components apart from guidance.

KEYWORDS
active ingredient, change mechanism, common and specific factor, e-health, guidance, psychotherapy

1 | INTRODUCTION

Anxiety disorders are among the most common groups of mental disorders (Steel et al., 2014). They are associated with high socioeconomic costs (Smit et al., 2006) and have a negative impact on psychosocial functioning (Craske & Stein, 2016) as well as on quality of life (Mendlowicz & Stein, 2000). Available treatments for these disorders are individual psychotherapy and/or pharmacotherapy (Cuijpers et al., 2013), with cognitive behavioral therapy (CBT) offering the largest evidence-base so far (Hofmann & Smits, 2008). Yet, the majority of patients suffering from anxiety disorders does not access adequate treatment (Wittchen & Jacobi, 2005), due to different structural and individual treatment barriers (Andrade et al., 2014).

Internet- and mobile-based interventions (IMIs) might provide solutions to several treatment barriers by combining the advantages of time- and space-independent delivery, potential anonymity, as well as low intervention costs and scalability for large numbers of patients (Andersson & Titov, 2014). Thereby, most IMIs make use of an Internet-based self-help approach, often grounded on empirically supported psychological treatment models such as CBT, combined with different degrees of human support involving text-based and asynchronous communication (Ebert et al., 2018). The type of support

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offered by "e-coaches" (i.e., health professionals, trained lay persons or peers) might range from basic tasks such as providing technical assistance or reminders, to more complex functions such as crisis management or therapeutic process work (Proudfoot et al., 2011). Internet-based interventions have been found to be efficacious in the treatment of anxiety disorders in the short and long term (Arnberg, Linton, Hultcrantz, Heintz, & Jonsson, 2014; Olthuis, Watt, Bailey, Hayden, & Stewart, 2016) with comparable outcomes to face-to-face psychotherapy (Andersson, Cuijpers, Carlbring, Riper, & Hedman, 2014). More recent approaches focus also on interventions optimized for smartphones or tablets, although the evidence-base for these mobile health applications (apps) is currently limited (Sucala et al., 2017).

Despite the indications that IMIs for adult anxiety disorders are efficacious, little is known about the intervention components that are responsible for therapeutic change. To date, only human support (i.e., "guidance" by e-coaches) as active component has attracted substantial research attention. In a systematic review of Baumeister, Reichler, Munzinger, and Lin (2014), guided interventions were superior to completely unguided interventions with a significant pooled standardized mean difference of −0.27 (95% CI [−0.45, −0.10]; $k = 8$ studies) in regard to symptom severity across mental disorders (depression $k = 3$, social phobia $k = 3$, insomnia $k = 1$, and eating disorders $k = 1$). The positive effect of guidance on symptom severity and adherence is established also in Internet interventions specific for depression (Richards & Richardson, 2012; Titov, 2011). However, further research is needed to determine whether the efficacy of IMIs for anxiety disorders depends on guidance-specific factors, such as the qualification of e-coaches, the timing of interactions, or the type and intensity of human support. Moreover, research efforts need to go beyond the narrow focus on guidance and take a more holistic view on different components of IMIs for anxiety disorders into account.

One approach to examine the incremental effects of distinct intervention components is to directly compare variations of IMIs in trials with a randomized controlled design. *Additive design* or *dismantling studies* could be used by either adding or subtracting specific elements of an intervention and therefore allow to experimentally investigate the incremental (add-on) effects of specific components of an IMI (Borkovec & Costonguay, 1998). Proponents of specific intervention factors suggest that psychotherapy operates primarily by these theory-driven specific factors described in treatment manuals (e.g., cognitive restructuring or exposure), whereas proponents of common factors suggest that psychotherapy is effective primarily because of factors common across treatments (e.g., therapeutic alliance or expectations) (Cuijpers, Reijnders, & Huibers, in press; Mulder, Murray, & Rucklidge, 2017). To test the role of specific and common factors, Stevens, Hynan, and Allen (2000) proposed an approach to compare complete treatments with *common factor controls* that are at best structural equivalent to the complete treatment and are considered as credible by the patients, but do not contain the specific factors and components delivered in the complete treatment package. Often such controls are designated as "attention placebos" or active control groups (e.g., discussion groups). The latter approach of psychotherapy research is suitable to make the case for the working function of specific intervention factors in IMIs as a package (general efficacy); the former approach might disclose information about the incremental effects of specific IMI components as stand-alone elements.

The importance of scientific knowledge about the active ingredients of IMIs responsible for therapeutic change can be highlighted with several points. First, information about the core components of treatments and their associated mediators might contribute to the verification of nosological theories of disorders (Kazdin, 2007). Second, uncovering the mechanisms of change is crucial for the refinement of intervention packages and optimization of treatment outcomes (Kazdin, 2007). Third, a comprehensive evidence-base on active components is central for the (cost-)efficient implementation and dissemination of IMIs, as interventions can be designed parsimoniously with efficacious intervention components alone (Bell, Marcus, & Goodlad, 2013). Furthermore, high technical standardization and methodological opportunities in research on Internet interventions might yield findings that also add to the long-lasting debate between proponents of specific versus common factors in psychotherapy research (Mulder et al., 2017). Finally, evidence resulting from experimental component studies is more robust in contrast to research on mediators, which is most often indirect and correlational, not allowing for causal inferences (Cuijpers, Cristea, Karyotaki, Reijnders, & Hollon, 2017).

To our knowledge, this is the first comprehensive systematic review aimed at summarizing, evaluating, and meta-analytically integrating research on intervention components of IMIs for adult anxiety disorders. The following three main research questions guided the conduction of this meta-analysis: (a) Are IMIs for anxiety disorders more efficacious than common factor controls? (b) Which intervention components are responsible for the efficacy of IMIs for anxiety disorders? (c) Which intervention components are associated with greater or lesser treatment adherence?

2 | METHODS

This meta-analytic review is in line with the recommendations of the PRISMA statement (Moher et al., 2009) and is registered with PROSPERO (CRD42017068268). Further detailed information on the conceptualization and methodology of this review are provided in the study protocol (Geßlein, 2017) and in the Supporting information online.

2.1 | Inclusion criteria

Studies were eligible for inclusion if they fulfilled the following eight criteria: (a) Adults (≥18 years); (b) at least one of the following anxiety disorders diagnosed at baseline: specific phobia (SP), social anxiety disorder (SAD), panic disorder (PD), agoraphobia (A), or generalized anxiety disorder (GAD); (c) IMI; (d) psychotherapeutic orientation; (e) active online control group, or additive or dismantling design study; (f) anxiety symptom severity (postintervention and follow-up) or adherence (completed modules and completer rate following Donkin et al., 2011); (g) randomized controlled trial; (h) peer-reviewed publication written in English or German.

2.2 | Information sources and search strategy

The Cochrane Central Register of Controlled Trials (CENTRAL), Embase, PsycINFO, PSYNDEX, and MEDLINE were searched separately to identify relevant studies, from database inception to April 2017 (detailed information of all search strings can be found in the Supporting Information). Additionally, the WHO International Clinical Trials Registry Platform (ICTRP) was searched for trials with preliminary/published results. The reference lists of included studies were hand searched to retrieve additional studies.

2.3 | Study selection and data extraction

The titles and abstracts yielded by the systematic database search were screened (HG), and obviously irrelevant records were removed. Afterward, the full texts of all relevant records were assessed in terms of the aforementioned eligibility criteria independently by two reviewers (HG and RR). Disagreements were solved by discussion and consultation of a third reviewer (MD). The study selection process is illustrated in a PRISMA flow chart (Moher et al., 2009). Study data were extracted by one reviewer (HG) and checked for integrity by another reviewer (MD).

2.4 | Risk of bias assessment

The methodological quality of included studies was rated according to the Cochrane risk of bias assessment tool (Higgins et al., 2011) independently by two reviewers. Studies were rated as having "low," "unclear," or "high risk" of bias on the following items: (a) random sequence generation, (b) allocation concealment, (c) blinding of participants and personnel, (d) blinding of outcome assessment, (e) incomplete outcome data, (f) selective reporting, and (g) other bias. Disagreements between reviewers (HG and RR) were solved by discussion and consultation of a third reviewer (MD).

2.5 | Data synthesis

Statistical analyses were performed using Review Manager 5.3 (The Cochrane Collaboration, 2014) and Stata, version 14 (StataCorp., 2015). If sufficient data were available to be pooled together (at least three trials), separate meta-analyses were conducted for each comparison as well as each outcome. In case of more than two relevant intervention groups per study, we followed the recommendations of the Cochrane Collaboration for combining multiple groups to create single pair-wise comparisons (Higgins & Green, 2011).

For continuous outcomes, standardized mean differences (*SMDs*) with 95% confidence intervals (95% CI) were calculated. Hedges' *g* was employed, as it corrects for biases due to small sample sizes (Borenstein, 2009). For dichotomous outcomes, odds ratios (*OR*) with 95% CI were calculated. To compute overall estimates of treatment outcomes, random-effects meta-analyses were performed to account for between-study heterogeneity.

To assess the degree to which statistical heterogeneity in the meta-analyses is caused by between-study differences, rather than due to chance, the I^2-statistic and Cochran's *Q* (with corresponding *P* values) were employed (Higgins & Thompson, 2002). Furthermore, forest plots were used for a visual representation of the presence and nature of statistical heterogeneity. In case of sufficient studies per meta-analysis, we intended to perform subgroup analyses (at least three trials per subgroup) and to determine the possible influence of publication bias by inspection of funnel plots (at least 10 trials; Higgins & Green, 2011).

3 | RESULTS

The electronic database search revealed 3,370 records. After removing duplicates and screening titles and abstracts, 159 full-text articles were assessed for eligibility. Finally, we included 34 studies (Andersson, Carlbring, & Furmark, 2012; Andersson, Paxling, et al., 2012; Berger et al., 2011; Boettcher, Aström, et al., 2014; Boettcher, Berger, & Renneberg, 2012; Boettcher, Hasselrot, et al., 2014; Butler, Mobini, Rapee, Mackintosh, & Reynolds, 2015; Carlbring, Ekselius, & Andersson, 2003; Carlbring et al., 2011; Christensen et al., 2014; Dagöö et al., 2014; Dear et al., 2015, 2016; Fogliati et al., 2016; Furmark et al., 2009; Gershkovich, 2016; Ivanova et al., 2016; Johansson et al., 2013; Johnston, Titov, Andrews, Spence, & Dear, 2011; Klein et al., 2009; Klein, Richards, & Austin, 2006; LaFreniere & Newman, 2016; Nordgren et al., 2014; Nordmo et al., 2015; Oromendia, Orrego, Bonillo, & Molinuevo, 2016; Richards, Klein, & Austin, 2006; Robinson et al., 2010; Schulz et al., 2016; Tillfors et al., 2008; Titov, Andrews, Choi, Schwencke, & Johnston, 2009; Titov, Andrews, Choi, Schwencke, & Mahoney, 2008; Titov, Andrews, Schwencke, et al., 2009; Titov et al., 2010) with 3,724 participants in this systematic review. The study selection process is outlined in the PRISMA flow chart (Figure 1).

3.1 | Characteristics of included studies

The main characteristics of included studies are summarized in Supporting Information Table 1. Of the 34 eligible studies, 16 investigated SAD, six PD/A, five GAD, and seven included more than one anxiety disorder. The majority of studies ($k = 32$) recruited their participants from community settings. In 32 trials, an interview was used as screening instrument (ADIS-IV, SCID-I, and/or MINI).

Altogether, 21 different components were assessed with 80 intervention groups. The majority of intervention groups had some form of guidance ($k = 67$), with eight trials providing guidance only on demand. For 23 intervention groups, additional peer support was reported.

The results of the risk of bias assessment are detailed in Figure 2. Inter-rater reliabilities between the two independent reviewers were adequate (Cohen's Kappa > 0.80 for all risk of bias domains). The items blinding of participants/personnel and outcome assessment on symptom severity were least met by the studies. Of note, blinding of participants in psychotherapy research is difficult to achieve, and we rigorously rated self-reported data in outcome assessment with "high risk of bias" accordingly.

The results of all meta-analytical comparisons are detailed in Table 1 and displayed in forest plots in Supporting Information Figure 1. If less than three studies provided information on outcomes to be

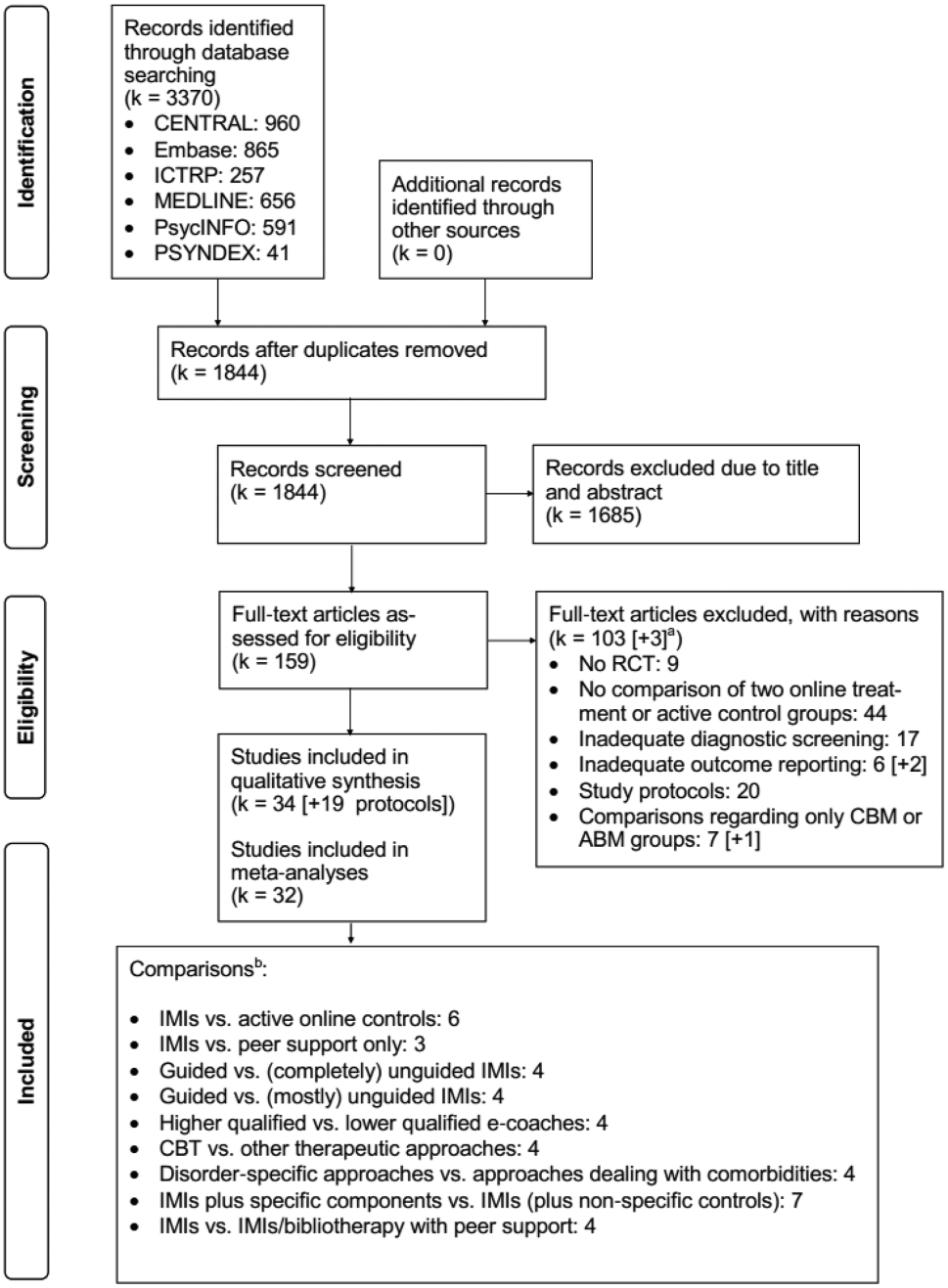


FIGURE 1 PRISMA flow chart

meta-analytically pooled together, the results of single studies are not reported here, except for the comparison of frequent versus infrequent guidance, and scheduled guidance versus guidance on demand. Overall, we were able to perform random-effects meta-analyses on 19 comparisons.

3.2 | General efficacy of IMIs compared to common factor controls

3.2.1 | IMIs versus active online control groups

A random-effects meta-analysis revealed a large effect size in favor of IMIs compared to active online controls for reducing anxiety symptoms at postintervention (six studies; *SMD* of −1.67 [95% CI: −2.93, −0.42]; Supporting Information Figure 1.1), with high statistical heterogeneity (I^2 = 94%) (Christensen et al., 2014; Johansson et al., 2013; Klein et al., 2006; LaFreniere & Newman, 2016; Nordgren et al., 2014; Richards et al., 2006).

3.2.2 | IMIs versus online peer support only

The meta-analysis for symptom severity at postintervention assessment yielded a medium effect size (three studies; *SMD* of −0.69 [95% CI: −0.98, −0.40]) in favor of IMIs compared to online peer support only (i.e., online forums; Supporting Information Figure 1.2), with moderate heterogeneity (I^2 = 34%) (Andersson, Carlbring, et al., 2012; Boettcher, Aström, et al., 2014; Carlbring et al., 2011).

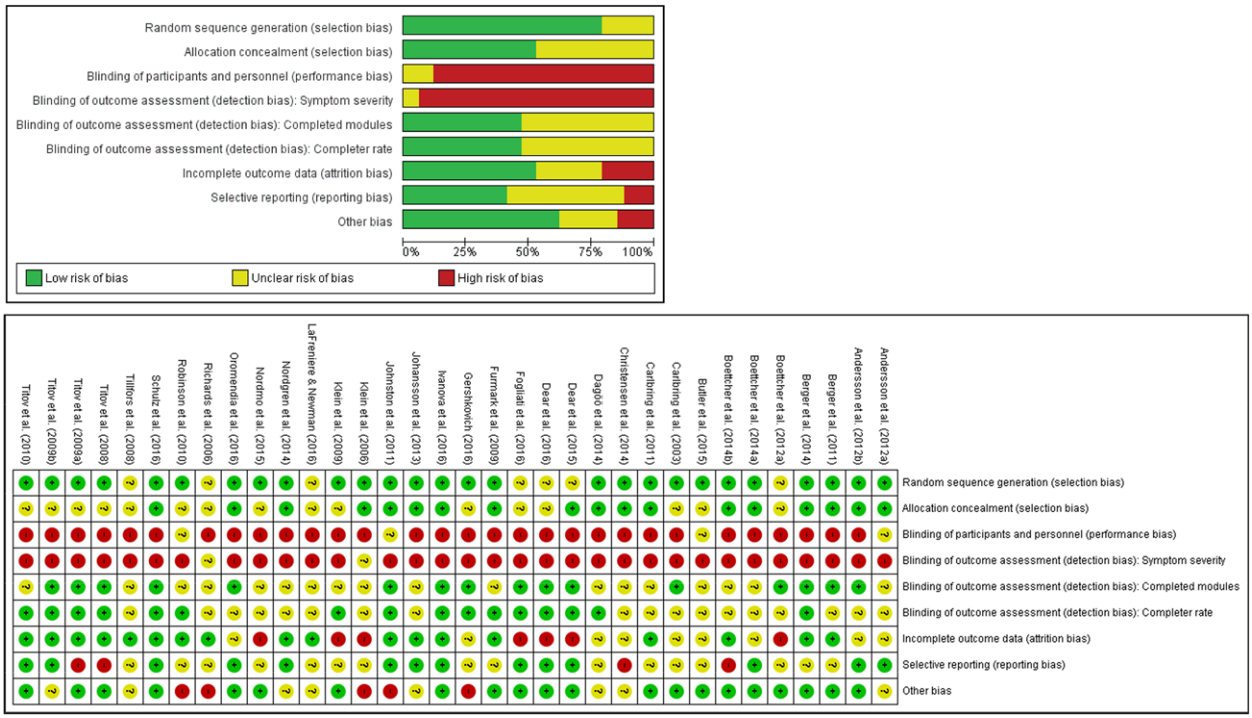


FIGURE 2 Risk of bias assessment

3.3 | Incremental effects of single intervention components

IMIs with different degrees of therapeutic support were divided into *completely* unguided interventions (i.e., self-help, with therapist contact for assessment at most), *mostly* unguided interventions (i.e., predominantly self-help, with additional technical guidance on demand, for example), and guided interventions (i.e., with continuous therapeutic support) following the definition of Newman and colleagues (Newman, Szkodny, Llera, & Przeworski, 2011).

3.3.1 | Guided versus completely unguided interventions

Guided IMIs were superior to *completely* unguided self-help versions of the same intervention with a small effect size (four studies; *SMD* of −0.39 [95% CI: −0.59, −0.18]) and low statistical heterogeneity ($I^2 = 0\%$; Supporting Information Figure 1.3) (Berger et al., 2011; Ivanova et al., 2016; Titov, Andrews, Choi, et al., 2009; Titov et al., 2008). In regard to adherence measures, guided IMIs resulted both in higher numbers of completed modules (four studies; *SMD* of 0.38 [95% CI: 0.10, 0.66]; Supporting Information Figure 1.4) and higher completer rates (three studies; *OR* of 2.56 [95% CI: 1.20, 5.43]; Supporting Information Figure 1.5).

3.3.2 | Guided versus mostly unguided interventions

Guided IMIs and *mostly* unguided interventions revealed no significant differences on symptom severity at postintervention (four studies; *SMD* of −0.02 [95% CI: −0.20, 0.16]) and follow-up (three studies; *SMD* of −0.02 [95% CI: −0.18, 0.13]) with marginal heterogeneity in both comparisons (I^2 = 21% and 0%; Supporting Information Figures 1.6 and 1.7) (Dear et al., 2015, 2016; Fogliati et al., 2016; Gershkovich, 2016). However, guided IMIs resulted in higher number of completed modules (*SMD* of 0.19 [95% CI: 0.01, 0.38]) and closely missed statistical significance for completer rate (*OR* of 1.35 [95% CI: 0.98, 1.86]). Statistical heterogeneity of these two meta-analyses was low to minimal (I^2 = 30% and 6%; Supporting Information Figures 1.8 and 1.9).

3.3.3 | Frequent versus infrequent guidance

Only one study (Klein et al., 2009) compared frequent (i.e., at least three e-mails per week) with infrequent guidance (i.e., one e-mail per week) with comparable results between trial groups (symptom severity at postintervention assessment: $g = 0.09$ [95% CI: −0.46, 0.64]; and completer rate: *OR* = 1.40 [95% CI: 0.41, 4.71]).

3.3.4 | Scheduled guidance versus guidance on demand

Two studies compared scheduled guidance (i.e., weekly scheduled e-mail [Berger et al., 2011] or telephone guidance [Oromendia et al., 2016]) with guidance on demand. In the study of Berger and colleagues, symptom severity at postintervention ($g = -0.12$ [95% CI: −0.65, 0.42]) and follow-up ($g = 0.03$ [95% CI: −0.50, 0.57]) did not differ significantly between these two trial groups. Likewise, the mean number of completed modules was comparable ($g = -0.10$ [95% CI: −0.66, 0.46]). In contrast, Oromendia and colleagues found significant add-on effects on symptom severity at postintervention ($g = -0.83$ [95% CI: −1.42, −0.24]), symptom severity at follow-up ($g = -0.71$ [95% CI: −1.29, −0.12]), and mean number of completed modules ($g = 1.26$ [95% CI: 0.63, 1.88]), all favoring scheduled guidance.

3.3.5 | Higher versus lower qualified e-coaches

Pooled together, the effect size for symptom severity at postintervention assessment did not differ significantly between the groups

TABLE 1 Meta-analytical comparisons of intervention components

		Number of studies	Sample size	Meta-analysis			Heterogeneity			
				SMD	*P*	95% CI	*Q*	*P*	I^2 (%)	95% CI
IMIs vs. common factor controls										
IMIs vs. active online controls	Symptom severity (postintervention)	6	151 / 127	−1.67	0.009	−2.93, −0.42	85.03	0.00001	94	89.78, 96.62
IMIs vs. online peer support only	Symptom severity (postintervention)	3	169 / 173	−0.69	0.00001	−0.98, −0.40	3.02	0.22	34	0, 78.24
Incremental effects of intervention components										
Guided vs. completely unguided IMIs	Symptom severity (postintervention)	4	189 / 190	−0.39	0.0002	−0.59, −0.18	1.70	0.64	0	0, 84.69
	Completed modules	4	178 / 176	0.38	0.007	0.10, 0.66	4.80	0.19	38	0, 78.52
	Completer rate	3	162 / 163	2.56	0.01	1.20, 5.43	4.40	0.11	55	0, 87.00
Guided vs. mostly unguided IMIs	Symptom severity (postintervention)	4	332 / 324	−0.02	0.84	−0.20, 0.16	3.78	0.29	21	0, 87.85
	Symptom severity (follow-up)	3	316 / 313	−0.02	0.76	−0.18, 0.13	0.38	0.83	0	0, 89.60
	Completed modules	4	372 / 373	0.19	0.04	0.01, 0.38	4.28	0.23	30	0, 74.47
	Completer rate	4	372 / 373	1.35	0.06	0.98, 1.86	3.18	0.37	6	0, 85.55
Higher vs. lower qualified e-coaches	Symptom severity (postintervention)	4	174 / 196	0.13	0.23	−0.08, 0.33	2.11	0.55	0	0, 84.69
	Completer rate	3	132 / 136	0.89	0.69	0.50, 1.57	0.65	0.72	0	0, 89.60
CBT vs. other therapeutic approaches	Symptom severity (postintervention)	4	90 / 91	−0.14	0.35	−0.43, 0.15	2.76	0.43	0	0, 84.69
Disorder-specific vs. transdiagnostic approaches	Symptom severity (postintervention)	3	315 / 314	−0.01	0.93	−0.16, 0.15	0.32	0.85	0	0, 89.60
	Symptom severity (follow-up)	3	315 / 314	−0.13	0.10	−0.29, 0.03	1.24	0.54	0	0, 89.60
	Completed modules	3	347 / 356	−0.03	0.70	−0.18, 0.12	0.11	0.95	0	0, 89.60
	Completer rate	3	347 / 356	0.84	0.27	0.61, 1.15	0.15	0.93	0	0, 89.60
IMIs vs. IMIs plus specific nononline intervention components	Symptom severity (postintervention)	7	229 / 244	−0.09	0.32	−0.27, 0.09	3.89	0.69	0	0, 70.81
IMIs vs. IMIs/ bibliotherapy with additional peer support	Symptom severity (postintervention)	4	182 / 174	−0.06	0.60	−0.26, 0.15	0.92	0.82	0	0, 84.69
	Completer rate	4	182 / 174	1.18	0.48	0.75, 1.87	0.50	0.92	0	0, 84.69

of higher (e.g., licensed psychologists with 2–3 years practical experience) versus lower qualified e-coaches (e.g., psychology students) with no statistical heterogeneity (four studies; *SMD*: 0.13 [95% CI: −0.08, 0.33]; $I^2 = 0\%$; Supporting Information Figure 1.10) (Andersson, Carlbring, et al., 2012; Johnston et al., 2011; Robinson et al., 2010; Titov, Andrews, Schwencke, et al., 2009). No difference was found in regard to completer rate (three studies; *OR* = 0.89 [95% CI: 0.50, 1.57]; Supporting Information Figure 1.11). Statistical heterogeneity was absent ($I^2 = 0\%$).

3.3.6 | CBT versus other therapeutic approaches

Four studies compared an IMI based on CBT principles with an intervention based on another therapeutic approach (psychodynamic therapy [Andersson, Paxling, et al., 2012], interpersonal therapy [Dagöö et al., 2014], and applied relaxation [Carlbring et al., 2003; Furmark et al., 2009]). The pooled effect size indicated no significant superiority of either of the examined interventions (*SMD* of −0.14 [95% CI: −0.43, 0.15]) with no statistical heterogeneity ($I^2 = 0\%$; Supporting Information Figure 1.12).

3.3.7 | Disorder-specific versus transdiagnostic approaches

Three studies (Dear et al., 2015, 2016; Fogliati et al., 2016) compared a transdiagnostic intervention (i.e., targeting symptoms of common mental disorders) with a disorder-specific intervention (targeting GAD, SAD, or PD). Pooled group differences regarding symptom severity at postintervention assessment (*SMD* = −0.01 [95% CI: −0.16, 0.15]; Supporting Information Figure 1.13), symptom severity at 6–12 months follow-up (*SMD* = −0.13 [95% CI: −0.29, 0.03]; Supporting Information Figure 1.14), mean number of completed modules (*SMD* = −0.03 [95% CI: −0.18, 0.12]; Supporting Information Figure 1.15), and completer rate (*OR* = 0.84 [95% CI: 0.61, 1.15]; Supporting Information Figure 1.16) were all nonsignificant. Statistical heterogeneity of the reported meta-analyses was absent ($I^2 = 0\%$).

3.3.8 | IMIs versus IMIs plus specific nononline intervention components

Seven additive design studies (Boettcher et al., 2012; Boettcher, Hasselrot, et al., 2014; Butler et al., 2015; Nordmo et al., 2015; Richards et al., 2006; Tillfors et al., 2008; Titov et al., 2010) with different nononline intervention components (e.g., stress management program) were included in this comparison. The meta-analysis of IMIs versus IMIs plus different specific nononline intervention components regarding symptom severity at postintervention assessment resulted in a nonsignificant *SMD* = −0.09 [95% CI: −0.27, 0.09] with no statistical heterogeneity ($I^2 = 0$; Supporting Information Figure 1.17).

3.3.9 | IMIs versus IMIs/bibliotherapy with additional peer support

Four studies (Furmark et al., 2009; Robinson et al., 2010; Schulz et al., 2016; Titov, Andrews, Schwencke, et al., 2009) compared an IMI with another IMI/bibliotherapy plus additional peer support (e.g., online forum). The meta-analysis for symptom severity at postintervention assessment resulted in a nonsignificant *SMD* of −0.06 [95% CI: −0.26, 0.15] with no heterogeneity ($I^2 = 0$; Supporting Information Figure 1.18). The meta-analysis for completer rate revealed no significant difference (*OR* = 1.18 [95% CI: 0.75, 1.87]; Supporting Information Figure 1.19). Statistical heterogeneity was absent ($I^2 = 0\%$).

3.4 | Subgroup analyses and assessment of publication bias

We planned to perform subgroup analyses for each comparison regarding type of anxiety disorder, psychotherapeutic approach, and guidance. This was not possible due to the low number of studies per subgroup, except for the comparison of IMIs versus IMIs plus specific nononline components in regard to guidance, which was not significant (Supporting Information Figure 1.17). The prespecified analyses to determine the possibility of publication bias were not feasible, because the number of studies in each comparison was too small.

4 | DISCUSSION

To our knowledge, this is the first meta-analytical review to summarize research experimentally investigating components of IMIs for anxiety. We identified 34 trials that compared IMIs to an active online control group, or compared IMIs varying in intervention components with 3,724 participants in total. Included primary studies examined 21 different intervention components in direct comparisons. In this review, we performed 19 meta-analyses of intervention components on symptom severity and treatment adherence. Thereby, IMIs for anxiety disorders achieved a large effect size (*SMD* = −1.67) when compared to active online control groups in reducing anxiety symptoms, and a medium effect size (*SMD* = −0.69) compared to peer support. This finding lends support for the active role of specific intervention components and indicates that the well-known efficacy of IMIs for anxiety disorders (Andersson et al., 2014; Arnberg et al., 2014; Olthuis et al., 2016) is not due to common (online) factors or a "digital placebo effect" alone (Torous & Firth, 2016). Among the intervention components examined in this review, only human support was associated with better treatment outcomes and higher adherence rates, when compared to *completely* unguided interventions. A finding that is consistent with results from other systematic reviews in IMIs focusing on common mental disorders (Baumeister et al., 2014) or depression alone (Richards & Richardson, 2012; von Rezori, Geßlein, Baumeister, & Domhardt, submitted), but is novel for the anxiety disorders, where previous subgroup analyses missed statistical significant incremental effects of guidance (Baumeister et al., 2014; Olthuis et al., 2016).

The adherence-facilitating function of guidance is further illustrated by the comparison of guided and *mostly* unguided interventions, although no effect of additional human support on anxiety symptoms emerged. The nonsignificance in this contrast might be explained by the amount of minimal guidance in the group of *mostly* unguided interventions, which might have leveled out the impact of human support in this comparison. Moreover, research-related contact with participants can be seen as a form of guidance of its own, which might further compensate the effect of the lesser extent of human support provided by the *mostly* unguided intervention itself.

We further reviewed other guidance-specific factors, but due to the low number of eligible studies, no meta-analyses were possible for frequency and scheduling of guidance. The meta-analytical comparison in regard to qualification of e-coaches suggests that the clinical expertise of e-coaches does not influence outcomes; a finding that is in line with previous reviews on other mental disorders (Baumeister et al., 2014; Titov, 2011). It seems likely that lower qualified e-coaches are as efficacious as higher qualified e-coaches, when they are supervised or able to refer nonresponding participants to a clinician. This finding might further support the aptitude of IMIs to cost-effectively scale up service supplies for anxiety disorders, as additional human support might require less clinical expertise than in other psychological treatments. However, this conclusion might not hold true in our underresourced health care reality, where lay personal might inadequately respond to critical situations, such as increased risk of suicide (Baumeister, 2017).

A main intention with this meta-analytic review was to provide a comprehensive overview of intervention components in IMIs for the anxiety disorders beyond guidance. First, in the meta-analyses of IMIs with different therapeutic approaches, all interventions were similarly efficacious in reducing anxiety symptoms at postintervention assessment; a finding that mirrors comparative outcome studies of conventional face-to-face psychotherapies for SAD (Mayo-Wilson et al., 2014). Of note, because this comparison is based on only four trials, which are seriously underpowered to detect possible differences, it is too early to draw firm conclusions on the differential efficacy of IMIs with divergent psychotherapeutic backgrounds. Second, transdiagnostic approaches were as efficacious when compared to disorder-specific interventions; therefrom, these generic interventions might further provide means to expand the range of evidence-based treatments for common mental disorders on a population scale. Third, IMIs with an additional nononline component or additional peer support were as efficacious as interventions without this component; a finding that is

TABLE 2 Key findings and recommendations for future research

Key findings

- IMIs for anxiety disorders were more efficacious than common factor controls, proposing an active role of different specific factors
- Guided IMIs were superior to completely unguided interventions and improved adherence
- Qualification of e-coaches was not associated with efficacy
- Transdiagnostic approaches were similar efficacious than disorder-specific approaches
- More research is needed, to determine which intervention components and associated mediators are responsible for therapeutic change

Recommendations for future research

- Research efforts toward identifying the active ingredients of Internet interventions would substantially profit from standardized definitions and classifications of intervention components, similar to taxonomies of behavior change techniques in health psychology (Abraham & Michie, 2008; Michie, Abraham, Whittington, McAteer, & Gupta, 2009; Michie et al., 2013). This would allow for more valid and reliable examinations of components between studies
- Further advancement of theories on the processes responsible for therapeutic change can inform and guide future research, whereas a comprehensive model of the mechanisms of change in IMIs for anxiety is currently lacking
- Future component studies should strive to accomplish sample sizes sufficiently powered to detect small (to very small) incremental effects of distinct intervention components, as these might be considered as clinically significant when pieced together
- Alternative approaches to identify active ingredients of IMIs might be the application of the Multiphase Optimization Strategy (MOST) and the Sequential Multiple Assignment Randomized Trial (SMART), using fractional factorial designs (Collins, Murphy, & Strecher, 2007)
- It would be timely to investigate other intervention components that could have not been meta-analytically evaluated in this review, such as frequency and scheduling of guidance, prompts, interactive elements, mode of delivery, or design factors
- It would be worthwhile to extend the evidence-base of additive design or dismantling studies of mobile health applications, considering a marked underrepresentation of component studies in these interventions

in line with some component studies in face-to-face psychotherapy (Cuijpers et al., 2017).

The present study has several strengths, including adherence to a registered study protocol, rigorous selection of studies, relatively high quality of included trials, as well as little heterogeneity across most meta-analyses and the comprehensive scope on intervention components. However, there are also important limitations. First, some primary studies were not sufficiently powered to detect even a medium effect size (i.e., below the needed number of 50 participants per group). Thus, it is possible that the nonsignificance in some comparisons might be primarily due to the small sample sizes of included studies, which is a common problem of component studies in psychotherapy research (Bell et al., 2013; Cuijpers et al., 2017). However, if we move forward to incremental effects of single components, small to very small add-on effects might already be regarded as clinically significant, and sample sizes should be calculated accordingly. Second, because of the small number of eligible studies, we were not able to perform subgroup analyses and test for publication bias as intended.

TABLE 3 Practical implications for intervention development and clinical practice

Evidence of intervention components in primary studies	Recommendations for intervention development and clinical practice
Guided interventions were significantly more efficacious and improved adherence when compared to completely unguided interventions (consistent evidence in four studies)	Consider to integrate some type of guidance. However, completely self-guided interventions might have a potential for scaling-up evidence-based interventions for common mental disorders, despite their smaller effect sizes
Qualification of e-coaches was not associated with efficacy (consistent evidence in four studies)	Although the qualification of e-coaches might not be associated with outcome, we strongly recommend e-coaching provided by health care professionals for two reasons: first, guidance in real-world settings might not be as controlled as in trials, which might also have an impact on the quality of e-coaching in relation to the qualification level of the e-coach (Baumeister, 2017). Second, there is limited evidence on adverse events in relation to varying qualification levels. Risk and not benefit should be the primary outcome when it comes to scaling down qualification levels in our health care services system
Frequency of guidance was not associated with efficacy (one study)	Increasing guidance over a certain threshold might not lead to further gains. Consider to integrate (short) weekly guidance or feedback once per module
Scheduling of guidance (inconsistent findings; two studies)	Further studies are necessary to draw clear conclusions in regard to scheduling of guidance; as such, no recommendations can be provided currently
Different therapeutic approaches were equally efficacious (consistent evidence in four studies)	Adhere to evidence-based therapeutic backgrounds/techniques for anxiety that are suitable for an Internet- and/or mobile-based setting
Transdiagnostic approaches were similar efficacious than disorder-specific IMIs (consistent evidence in three studies)	Consider to resort to transdiagnostic protocols, in order to reach larger number of patients with the same intervention, as long as potential users are still attracted by the (more generic) intervention
Adding a nononline component to full-featured IMIs did not increase efficacy (consistent evidence in seven studies)	Find an appropriate balance of the number of components of treatment packages, thereby maximizing efficacy, but minimizing costs in regard to patients' time and strain, as potential risk factors for attrition
Adding peer support to full-featured IMIs did not increase efficacy (consistent evidence in four studies)	Offering peer support might foster the acceptability and approval of IMIs, but might not increase efficacy

Third, no corrections for multiple comparisons were applied and no equivalence margin was specified a priori; thus, statistical inferences should be considered attentively. Fourth, we preferred self-report instruments measuring general anxiety symptoms (e.g., the Beck Anxiety Inventory, BAI) over instruments measuring disorder-specific symptoms. Yet, the BAI has been criticized for measuring primarily physiological symptoms and might reflect changes in cognitive symptoms not sufficiently (Leyfer, Ruberg, & Woodruff-Borden, 2006). Fifth, the vast majority of included trials focused on Internet-based interventions, implying a considerable underrepresentation of component studies in mobile-based interventions. Sixth, we did not perform additional forward searches as recommended by the Cochrane Collaboration (Higgins & Green, 2011). Whereas an empirical study of the impact of forward searches on search sensitivity indicates that it might not be the "best use of valuable time and resources" (Wright, Golder, & Rodriguez-Lopez, 2014), suggesting that our elaborated search likely already sensitively covered the review topic.

Based on the findings of this review, several recommendations for future research (Table 2) and implications for intervention improvement as well as clinical practice (Table 3) can be delineated. When reading the clinical implications, the reader should bear in mind the small evidence-base and limited statistical power of the present component studies. Additionally, small incremental effects of single intervention components are not detectable until very large sample sizes are realized. Hence, converging empirically supported recommendations can be derived from findings of primary studies, which at least can inform clinical practice what likely might work.

5 | CONCLUSIONS

The results of this meta-analytic review suggest that the efficacy of IMIs for anxiety disorders is not reliant on common (online) factors alone. Among several specific intervention components examined though, only guidance revealed incremental effects as stand-alone element. As such, these findings might mainly mirror the limited evidence-base of component studies so far, precluding further conclusions widely. Therefrom, more high-quality research is urgently needed to determine which components and associated mediators are essential, in order to inform our understanding of the mechanisms of therapeutic change in these innovative interventions more solidly. It seems likely that studies with sufficient power would reveal incremental effects of other components apart from guidance, similarly to meta-analyses on IMIs for depression (Von Rezori et al., submitted) or psychological treatments in general (Bell et al., 2013). These future studies might also highlight the role of combined treatment packages, with several (specific and nonspecific) active ingredients simultaneously at play (Cuijpers et al., in press). Overall, the evidence-base of IMIs for anxiety disorders is on the rise, implicating numerous possibilities for mental health care and pointing to a relevant potential to scale up mental health services for common mental disorders worldwide (Ebert & Baumeister, 2017; Karyotaki et al., 2017).

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CONFLICT OF INTEREST

The authors declare that they have no conflicts of interest.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

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Part V

Mediators and mechanisms of change in digital interventions

Part V comprises the following chapters, published as:

Chapter 8. * Domhardt, M., Lutsch, A., Sander, L. B., Paganini, S., Spanhel, K., Ebert, D. D., Terhorst, Y., & Baumeister, H. (2023). Mediators of digital depression prevention in patients with chronic back pain: Findings from a multicenter randomized clinical trial. *Journal of Consulting and Clinical Psychology*. Advance online publication. https://doi.org/10.1037/ccp0000808

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Chapter 10. * Domhardt, M., Nowak, H., Engler, S., Baumel, A., Grund, S., Mayer, A., Terhorst, Y., & Baumeister, H. (2021). Therapeutic processes in digital interventions for anxiety: A systematic review and meta-analytic structural equation modeling of randomized controlled trials. *Clinical Psychology Review, 90*, 102084. https://doi.org/10.1016/j.cpr.2021.102084

Chapter 11. * Domhardt, M., Steubl, L., Boettcher, J., Buntrock, C., Karyotaki, E., Ebert, D. D., Cuijpers, P., & Baumeister, H. (2021). Mediators and mechanisms of change in internet- and mobile-based interventions for depression: A systematic review. *Clinical Psychology Review, 83*, 101953. https://doi.org/10.1016/j.cpr.2020.101953

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Chapter 8

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Mediators of Digital Depression Prevention in Patients With Chronic Back Pain: Findings From a Multicenter Randomized Clinical Trial

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Objective: The mechanisms of change in digital interventions for the prevention of depression are largely unknown. Here, we explored whether five theoretically derived intervening variables (i.e., pain intensity, pain-related disability, pain self-efficacy, quality of life [QoL], and work capacity) were mediating the effectiveness of a digital intervention specifically designed to prevent depression in patients with chronic back pain (CBP). ***Method:*** This study is a secondary analysis of a pragmatic, observer-masked randomized clinical trial conducted at 82 orthopedic clinics in Germany. A total of 295 adults with a diagnosis of CBP and subclinical depressive symptoms were randomized to either the intervention group ($n = 149$) or treatment-as-usual ($n = 146$). Longitudinal mediation analyses were conducted with structural equation modeling and depression symptom severity as primary outcome (Patient Health Questionnaire–9 [PHQ-9]; 6 months after randomization) on an intention-to-treat basis. ***Results:*** Beside the effectiveness of the digital intervention in preventing depression, we found a significant causal mediation effect for QoL as measured with the complete scale of Assessment of Quality of Life (AQoL-6D; axb: −0.234), as well as for the QoL subscales mental health (axb: −0.282) and coping (axb: −0.249). All other potential intervening variables were not significant. ***Conclusion:*** Our findings suggest a relevant role of QoL, including active coping, as change mechanism in the prevention of depression. Yet, more research is needed to extend and specify our knowledge on empirically supported processes in digital depression prevention.

What is the public health significance of this article?
Digital interventions are effective in preventing depression and can make an important contribution to public health. Although information on the mechanisms of change is crucial to improve interventions, knowledge how these interventions work is largely pending. This study indicated that quality of life and active coping were significantly conveying the effects of a digital intervention for the prevention of depression in patients with chronic back pain.

Keywords: chronic pain, depression, psychotherapy, digital health, mechanism of change

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Chronic back pain (CBP) is an important risk factor for major depression (IsHak et al., 2018; Thom et al., 2019). These two conditions often occur together, are associated with extensive detrimental effects on health and are among the main contributors to the global burden of disease (Rice et al., 2016; Vos et al., 2016). Moreover, when patients with CBP develop a comorbid major depressive episode, more adverse outcomes are probable, because depression is associated with impaired pain management (Bair et al., 2003),

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continued

prolonged time to recovery from chronic pain (Costa et al., 2009), and increased risk for suicidal ideation and behavior (Cheatle, 2011; Racine, 2018). Therefore, preventing the onset of major depression is particularly important in patients with CBP and is considered as a global public health priority in general (Cuijpers et al., 2012; Ebert & Cuijpers, 2018; Muñoz & Bunge, 2016).

Psychological interventions are effective in preventing depression (Cuijpers et al., 2021; van Zoonen et al., 2014) and also yield positive effects on pain-related outcomes in patients with chronic pain, like pain management (Vitoula et al., 2018; Williams et al., 2020). Yet, evidence-based interventions for the prevention of depression that are conducted face-to-face are rarely integrated into routine care for patients with CBP, since health care systems are often fragmented, overlooking the intertwined nature of mental and physical health conditions (Foster et al., 2018). This treatment fragmentation is an important obstacle for the accessibility of depression prevention in patients with CBP, impeding the proficiency and efficiency of health care services for this vulnerable patient group (Saxena et al., 2007; van Zoonen et al., 2014).

Digital interventions for the prevention of common mental disorders are a promising approach to close this gap, as they can be provided free from the restraints of travel and time, are potentially scalable for large numbers of persons, and can overcome treatment fragmentations (Domhardt et al., 2019; Rigabert et al., 2020). Digital interventions—which are most often based on cognitive behavioral therapy (CBT) principles—are found to be efficacious in both preventing (Buntrock et al., 2016; Ebert et al., 2017; Reins et al., 2021; Sander et al., 2016) and treating depression in adults (Karyotaki et al., 2021; Königbauer et al., 2017; Moshe et al., 2021). Additionally, there are first encouraging indications that these novel interventions are also effective in preventing depression onset in the specific population of patients with CBP (Sander et al., 2020). A randomized clinical trial (RCT) conducted in routine orthopedic aftercare indicated that the digital intervention reduced the risk of a depression onset in patients with CBP within a 12-month follow-up period by 52% (assessed with SCID-5 interview; hazard ratio: .48, 95% CI [.28, .81], $p < .001$; Sander et al., 2020). Furthermore, the CBT-based intervention was also effective in preventing depression symptom deterioration 9 weeks after randomization (linear regression analyses with Patient Health Questionnaire–9 [PHQ-9] as outcome: −.43, 95% CI [−.62, −.23]) and 6 months after randomization (−.28, 95% CI [−.49, −.07]) but did not reduce subjective pain intensity (9 weeks: −.25, 95% CI [−.47, .02]; 6 months: −.06, 95% CI [−.30, .18]; Sander et al., 2020). These findings suggest that digital CBT might contribute to improve the continuity of care following inpatient orthopedic rehabilitation for patients with CBP and might have an important role to play in the prevention of depression in this high-risk population.

However, the mechanisms of change in digital interventions for the prevention of depression are largely uncertain so far. Knowledge on the mediators and mechanisms of change in psychological (i.e., preventive and psychotherapeutic) interventions is of high scientific and clinical significance though. Because evidence-based information on the mechanisms of change can contribute to the refinement of interventions, highlighting pathways to develop more effective treatment packages with enhanced outcomes (Domhardt, Engler, et al., 2021; Domhardt, Nowak, et al., 2021). Mediation studies can help to gain a deeper and empirically based understanding of the mechanisms of change (i.e., the processes within persons that are induced by the intervention and lead to positive change in the outcome; Domhardt, Nowak, et al., 2021). At this, mediation studies examine whether a mediator variable statistically accounts for the relationship between an intervention and an outcome (Kraemer et al., 2002). Hereby, a mediator might point to—or is in the ideal case congruent with—a change mechanism but may also be a proxy for one or more other variables actually representative for the true mechanism (Kazdin, 2007). Hence, several other features and criteria (Kazdin, 2007) strengthen the aptitude to draw causal conclusions from mediation studies (e.g., research design with RCT, control group, $n \geq 40$ per group, theoretical deduction of mediators, and testing for multiple competing mediators), with the validation that the mediator changes before the outcome being of outmost importance (i.e., "temporal precedence," requiring at least three assessments of mediators and outcomes; Cole & Maxwell, 2003; Domhardt & Baumeister, 2021).

A comprehensive systematic overview on evidence-based mediators in digital psychotherapeutic and preventive interventions for depression was provided by the authors of the present article (Domhardt, Steubl, et al., 2021). In this review of 26 studies, a broad range of 64 distinct variables were investigated within cognitive, behavioral, affective, and other mediator domains, as well as within the domain of skills (Domhardt, Steubl, et al., 2021). In the subsample of interventions with a prevention focus (13 studies), mediators such as acceptance (Viskovich & Pakenham, 2020), coping self-efficacy (Bakker et al., 2018), emotion regulation

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The data set analyzed during the present mediation study (i.e., secondary analysis) is available from the corresponding author on reasonable request. The data set was originally generated during the effectiveness study of Sander et al. (2020).

Matthias Domhardt played lead role in conceptualization, validation and writing–original draft, supporting role in data curation, software and visualization and equal role in formal analysis and methodology. Arne Lutsch played supporting role in conceptualization, data curation, software, validation, writing–original draft and writing–review and editing and equal role in formal analysis and methodology. Lasse B. Sander played lead role in investigation, supporting role in conceptualization, data curation, resources and writing–review and editing and equal role in project administration. Sarah Paganini played supporting role in data curation, investigation and writing–review and editing. Kerstin Spanhel played supporting role in data curation, investigation and writing–review and editing. David D. Ebert played supporting role in project administration, supervision and writing–review and editing and equal role in funding acquisition. Yannik Terhorst played supporting role in conceptualization, formal analysis, software, validation and writing–review and editing and equal role in data curation and methodology. Harald Baumeister played lead role in funding acquisition, resources and supervision and supporting role in conceptualization and writing–review and editing.

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(Ma et al., 2018), reappraisal (Morris et al., 2015), or sense of autonomy (Auyeung & Mo, 2019) were found to be significant in conveying the intervention effects. Yet, the majority of these studies were limited by methodological shortcomings (especially in regard to the establishment of the temporal precedence), precluding causal conclusions widely (Domhardt, Steubl, et al., 2021). Moreover, to our knowledge, no RCT has investigated the mediators and mechanisms of change in interventions for the prevention of depression in patients with CBP to this point—neither in interventions that are implemented face-to-face (Moreno-Peral et al., 2020) nor by digital technology (Domhardt, Steubl, et al., 2021).

However, given the complex and intertwined nature of this comorbid constellation, different theoretically deduced mediators might be relevant in the (digital) prevention of depression in patients with CBP (Bair et al., 2003; Campbell et al., 2003), and both theoretical frameworks of CBT for depression (Beck et al., 1979) and pain treatment (Ehde et al., 2014) may come into play. In both conditions, an essential component of CBT is cognitive restructuring and the acquisition of functional cognitions, representing theorized core change mechanisms, such as perceived control, self-efficacy, or reduction in rumination (Garratt et al., 2007; Lemmens et al., 2016; Lorenzo-Luaces et al., 2015). In fact, prior research has demonstrated the significant mediating role of pain self-efficacy in face-to-face CBT for patients with different manifestations of chronic pain, both on depression symptoms (Arnstein et al., 1999) as well as on pain-related outcomes (Burns et al., 2020). Another central element of CBT is behavioral activation (Jacobson et al., 1996; Janssen et al., 2021), with the assumption that this intervention component exerts its effects by increasing pleasant and work-related activities, resulting in environmental reward and symptom reduction (Janssen et al., 2021). Indeed, there are indications that the ability to work and improvement in quality of life (QoL) may have relevant parts in therapeutic change on depression symptoms in patients with chronic pain (Bair et al., 2003; Gatchel et al., 2007; Williamson & Schulz, 1992; Wong et al., 2010). Furthermore, other conceptualized working mechanisms induced by behavioral activation for depression in patients with chronic pain are thought to evolve through decrease in pain intensity and pain-related disability (Arnstein et al., 1999; Bair et al., 2003; Brooks et al., 2019; Ehde et al., 2014), with reciprocal relationships between potential mediators and outcomes in some instances, pointing to a complex model of therapeutic change (Arnstein et al., 1999; Burns et al., 2020). Yet, as these theoretical considerations and empirical findings are derived from research on CBT conducted face-to-face, these potential mediators have yet to be empirically established for digital interventions, in which the self-management and active coping of patients are thought to be even more relevant (Domhardt & Baumeister, 2021).

The present mediational study is intended to contribute to the understanding of how psychological interventions for the digital prevention of depression in the specific population of patients with CBP work. As such, the central aim of this study was to investigate the role of five competing variables (i.e., pain intensity, pain-related disability, pain self-efficacy, QoL, and ability to work) as possible mediators and putative mechanisms of change in the aforementioned digital intervention to prevent depression in patients with CBP (Sander et al., 2020). Furthermore, by adhering to the methodological quality criteria for process research highlighted above, we intend to generate empirically supported information on change mechanisms with higher causal confidence.

Method

This mediation study is a secondary analysis of a pragmatic, observer-masked randomized clinical trial with a parallel design, called "PROD-BP—Prevention of Depression in Back Pain Patients" (Sander et al., 2017, 2020). Details on the methods of the original study are presented in the protocol (Sander et al., 2017) and in the effectiveness article (Sander et al., 2020). In the following, we provide essential information on the methods of the present mediational study, in line with the Consolidated Standards of Reporting Trials statements (Montgomery et al., 2018; Zwarenstein et al., 2008).

Procedure, Participants, and Intervention

The original effectiveness study received ethics approval from the institutional review board of the University of Freiburg (EK-297/14_150513) and was registered with the German Clinical Trial Register (DRKS00007960). The recruitment of participants was conducted at 82 orthopedic clinics across Germany via personal invitation (eight clinics) as well as letters and flyers after patient discharge (74 clinics) between October 2015 and July 2017. All participants were thoroughly informed about the study objectives and provided written informed consent.

Patients were eligible for the "PROD-BP" study, if they (a) were at least 18 years, (b) had a diagnosis of CBP (duration of at least 6 months), (c) had sufficient language skills, (d) had access to the internet, and (e) reported persistent subthreshold depressive symptoms with a screening score of 5 or higher on the PHQ-9 on two of three assessments in the past 3 months. Yet, patients (f) with a current or recent (past 6 months) major depressive disorder, (g) a current persistent depressive disorder, or (h) bipolar disorder (all assessed with the Structured Clinical Interview for the *Diagnostic and Statistical Manual of Mental Disorders*, fifth edition [SCID-5]; First et al., 2015) were excluded or referred to a parallel treatment trial, respectively (Baumeister et al., 2021). Additionally, patients (i) with an ongoing, past, or upcoming (waitlist) psychotherapy as well as patients (j) with acute suicidality were excluded.

Participants randomized to the intervention group received a guided, internet-based self-help intervention plus treatment-as-usual (TAU). Participants randomized to the control group received only TAU. As such, the participants of both groups had unrestricted access to all health care services, including possible medication.

The intervention was a guided self-help intervention grounded on CBT principles for the indicated prevention of depression. It was provided on an online platform and comprised six mandatory modules, three optional modules, and two booster sessions, with a duration of 45–60 min of each module. Sessions could have been repeated as often as desired. All modules consisted of information provided by text, audio, or video, as well as assignments, metaphors, and exercises.

Mandatory intervention content comprised "Psychoeducational information about prevention of depression," "Planning for regular behavioral activation," "Learning and training of problem solving skills," "Recognition and prevention of rumination," "Introduction

to mindfulness and acceptance," "Training of self-care and relaxation skills," "Integration of physical activity into daily life," and "Techniques to build robust self-esteem." Optional modules focused on "Healthy sleep," "Partnership and sexuality," and "Returning to the workplace."

The intervention components were thought to induce several theoretically based mechanisms of CBT interventions, for instance, behavioral activation, active coping, self-efficacy, or the usage of newly acquired skills. Emphasis was laid on homework assignments, which were intended to support the implementation of the learned skills into daily life. To enhance patient adherence and to reduce study attrition, interactive elements (e.g., quizzes or conditional content) were implemented. Additionally, patients were asked if they wanted to receive daily reinforcing text messages on their smartphones.

Participants were free to decide when to work on the booster sessions (within a time frame of 3 months) at the end of the last session. The main intention of the two booster sessions was to summarize and repeat the most important intervention content, as well as to invite participants to reflect on the application of the newly acquired skills in their daily lives. In specific, the content of the first booster session was a repetition of previous learned content (i.e., behavioral activation, pleasant activities, problem-solving). Furthermore, participants were invited to update their activity plan, practice their problem-solving skills, as well as to try new exercises (e.g., an additional mindfulness exercise). In the second booster session, participants were free to choose earlier intervention topics of their personal interest and had the opportunity to repeat the modules again. Last, participants were invited to reflect on what they have learned and which positive changes they have already achieved.

Throughout the intervention, trained and supervised psychologists provided written feedback within 24 hr after each completed session (the mean total guidance time per participant was 64.8 min, $SD = 47$). A more detailed description of the intervention content can be found in the study protocol (Sander et al., 2017). Details on the results of the effectiveness of the intervention to prevent depression are outlined in the previously published effectiveness article (Sander et al., 2020).

Measures

All measures were based on self-report and were collected using a secure, online-based assessment system. Assessments for the present study were conducted at baseline (T0), 9 weeks (T1), and 6 months (T2) after randomization. In the original effectiveness study (Sander et al., 2020), there was also an assessment at 12-month follow-up in order to detect possible depression onset throughout a longer period, which was not relevant to the current mediational study. Five potential mediator variables (i.e., pain intensity, pain-related disability, pain self-efficacy, QoL, and ability to work) were assessed next to the primary outcome.

Depression Symptom Severity

The primary outcome in this study was self-reported depression symptom severity assessed with the PHQ-9, in order to be able to grasp and evaluate a possible dimensional relationship between the mediator variables and depressive symptoms. The PHQ-9 is widely used as a self-administered screening instrument for depressive symptoms and has proven its reliability with a Cronbach's α of .86 (Kroenke et al., 2001). In contrast, the primary outcome in the original effectiveness study was the observer-masked rated time to onset of a major depressive episode over a 12-month follow-up period using the SCID-5 (First et al., 2015).

Pain Intensity

Pain intensity was measured with an 11-point numerical rating scale, assessing the average pain of the last week from 0 = *no pain* to 10 = *extremely intensive pain*. Additionally, a categorical rating scale on the average pain intensity of the last week with four classifications ("none," "mild," "moderate," and "severe") was applied in the original trial but was not used in this mediational study. The ratings of pain intensity (and pain-related disability) were measured in line with the Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials recommendations for core outcome measures in clinical trials for chronic pain (Dworkin et al., 2005, 2008).

Pain-Related Disability

Pain-related disability was assessed with the Oswestry Disability Index, which consists of 10 items. The index is a validated self-report questionnaire and was evaluated as reliable with a Cronbach's α of .90 (Mannion et al., 2006).

Pain Self-Efficacy

Pain self-efficacy was assessed with the Pain Self-Efficacy Questionnaire that comprises 10 items. It is a validated instrument and has shown to be reliable with a Cronbach's α of .93 (Nicholas, 2007).

Quality of Life

Health-related QoL was assessed with the Assessment of Quality of Life (AQoL-6D), which consists of 20 items assessing six dimensions (Richardson et al., 2012). The subscales are independent living (four items), mental health (four items), coping (three items), relationships (three items), pain (three items), and senses (three items). The AQoL-6D has shown to be reliable with a Cronbach's α of .89 (Allen et al., 2013).

Work Capacity

Work capacity was assessed with the German version of the Subjective Prognostic Employment Scale, a self-report questionnaire consisting of three items with high internal consistency (Guttman scaling: rep = .99; Mittag & Raspe, 2003).

Statistical Analyses

Structural equation modeling (SEM) was applied, as it is recommended in mechanisms of change research to assess longitudinal mediation effects (Cole & Maxwell, 2003; Falkenström et al., 2022). Possible mediation effects for each putative mediator were investigated separately (Preacher & Hayes, 2008), with group (intervention + TAU vs. TAU only) as the independent variable and depression symptom severity (PHQ-9) as the dependent variable. Structural

equation models were constructed in two steps: First, a measurement model was investigated containing the independent variable, a latent mediation factor (i.e., pain-related disability, pain self-efficacy, and QoL), and a latent depression factor. Correlations between all factors and manifest variables were allowed. Due to the structure of the measures of pain intensity and work capacity, these variables were treated as manifest variables. Based on sufficient goodness of fit (see criteria below) of the measurement model, mediation paths were investigated in a second step as follows: In order to principally infer a causal relationship, changes in the mediator must temporally precede changes in the dependent variable (Kazdin, 2007). Thus, we longitudinally assessed the mediator and dependent variables at baseline (T0) as well as at 9 weeks (T1) and 6 months (T2) after randomization.

Cole and Maxwell's (2003) recommendations to assess longitudinal mediation effects with SEM were followed. Before computing the mediation model, a measurement model for each mediator variable was saturated. First, an unconstrained model (paths were allowed to vary freely) was estimated, then tests of equivalence of various parameters of the latent variables over time were conducted by constraining factor variances, covariances, and their relations across waves. Stepwise, the constrained model was tested against the unconstrained model using χ^2 tests. Due to parsimony, the most restrictive model with the best model fit criteria was chosen. Only model tests for factorial invariance had significant improvements over the unconstrained models. Factorial invariance was assumed, implying that the relation of a latent variable to a manifest variable is constant over time. The factor loadings at the first assessment (T0) for all latent variables were constrained to equal their counterparts at subsequent assessments (T1, T2). All interim steps of the measurement model selection are displayed in Table 1.

To evaluate the model fit and to compare different models, established fit indices were considered. The root-mean-square error of approximation (RMSEA) as a noncentrality parameter and the standardized root-mean-square residual (SRMR) as a residual index were used because the χ^2 test tends to reject misspecified models too sensitively (Browne & Cudeck, 1992; Moshagen, 2012; Moshagen & Erdfelder, 2016). Cutoff values for an acceptable goodness of fit were based on standard modeling criteria: RMSEA < .06 and SRMR < .08 (Hu & Bentler, 1999). For further investigations of the structure and potential sources of misfit, modification indices were evaluated (MacCallum et al., 1992). Parameters were estimated using the full information maximum likelihood estimator (Enders, 2010). Effect sizes represent standardized β coefficients.

All statistical analyses were conducted according to the intention-to-treat principle. Missing data were assumed to be at random. The full information maximum likelihood estimator was applied in all models to handle missing values.

The software R was used for all analyses (R Core Team, 2016). For SEM, the R package "lavaan" (Version 0.6-8) was used as the core package (Rosseel, 2012).

Results

Participant Characteristics and Participant Flow

A total of 9,757 adults were recruited, of which 1,138 individuals were scheduled for the baseline telephone assessment, and 350 individuals were found eligible for inclusion and scheduled for online baseline assessment (the participant flowchart is depicted in Supplemental Figure A.1). The final sample consisted of 295 adult patients with CBP and subclinical depressive symptoms (n = 184 female [62%]; age: $M = 52.8$, $SD = 7.7$). The participants were randomly assigned to either the intervention group (149 participants; n = 89 female; age: M = 51.7, SD = 8.5) or control group (146 participants; $n = 95$ female; age: $M = 53.9$, $SD = 6.7$). Further details on the sample characteristics are displayed in Table 2.

Mediation Analyses

SEM was used to evaluate each mediator in a separate model. The independent variable for each mediation model was group at baseline, with no significant differences in the dependent variable depression symptom severity between the two groups at baseline, $t(284) = 0.10$; $p = .92$. χ^2 tests for model comparison for all three latent mediator variables were not significant (Table 1), indicating that the models with factorial invariance structure (Model 2) fit the data better than the unconstrained models (Model 1). Thus, Model 2 was selected as the measurement model for pain-related disability (RMSEA = .043, SRMR = .073), pain self-efficacy (RMSEA = .045, SRMR = .066), and QoL (RMSEA = .052, SRMR = .083).

The central results of the mediation analyses are displayed in Table 3. The structural equation models for the latent mediators indicated a good fit overall (for pain-related disability: RMSEA = .044, SRMR = .069; for pain self-efficacy: RMSEA = .051, SRMR = .067; for QoL: RMSEA = .057, SRMR = .082). Support

Table 1
Model Fit Comparison for Testing Factorial Invariance in the Latent Mediators

Mediator	Model	*df*	χ^2	p[a]	AIC	BIC	RMSEA	SRMR
Pain-related disability	Model 1	1,689	2,625.6		30,104	31,074	.043	.067
	Model 2	1,726	2,670.8	.1681	30,075	30,909	.043	.073
Pain self-efficacy	Model 1	1,689	2,721.7		33,929	34,899	.046	.064
	Model 2	1,725	2,754.5	.6202	33,890	34,727	.045	.066
Quality of life	Model 1	3,894	6,983.0		39,285	40,697	.052	.081
	Model 2	3,950	7,046.7	.2255	39,237	40,442	.052	.083

Note. Model 1 = model with no restriction; Model 2 = model with factorial invariance restriction over time; AIC = Akaike information criterion; BIC = Bayesian information criterion; RMSEA = root-mean-square error of approximation; SRMR = standardized root-mean-square residual.
[a] Nonsignificant p values indicate a good fit.

Table 2
Baseline Characteristics

Variable	Intervention group (n = 149)	Control group (n = 146)	Total sample (N = 295)
Sociodemographic characteristics			
Age, *M* (*SD*)	51.7 (8.5)	53.9 (6.7)	52.8 (7.7)
Male	60 (40.3)	51 (34.9)	111 (37.6)
Single	15 (10.1)	13 (8.9)	28 (9.5)
Married or in relation	107 (71.8)	111 (76.0)	218 (73.9)
Divorced or separated	21 (14.1)	16 (11.0)	37 (12.5)
Having kids	117 (78.5)	115 (78.8)	232 (78.6)
Educational level[a]			
Low	102 (68.5)	105 (71.9)	207 (70.2)
Middle	25 (16.8)	18 (12.3)	43 (14.6)
High	22 (14.8)	23 (15.8)	45 (15.3)
Previous therapy experience			
Only psychotherapy	21 (11.1)	17 (11.6)	38 (12.9)
Only medication	12 (8.1)	11 (7.5)	23 (7.8)
Psychotherapy and medication	20 (13.4)	23 (15.8)	43 (14.6)
Internet Affinity Scale (IAS)[b], *M* (*SD*)	8.99 (3.79)	8.63 (3.56)	8.81 (3.67)
Depressive symptom severity			
PHQ-9 score[c]	8.02 (3.43)	7.98 (3.78)	8.00 (3.60)

Note. PHQ = Patient Health Questionnaire. Values are either *M* (*SD*) or *n* (%).
[a] Educational level is based on the International Standard Classification of Education (low: Level 1–2, medium: Level 3–4, high: Level 5+). [b] Based on imputed data. IAS total score range: 0–20, with higher scores indicating high internet affinity. [c] Based on imputed data. PHQ-9 total score range: 0–27, with 0–4 indicating minimal depression, 5–9 indicating mild depression, 10–14 indicating moderate depression, 15–19 indicating moderately severe depression, and 20–27 indicating severe depression.

for a mediation effect was demonstrated only for QoL (Table 3 and Figure 1); all other putative intervening variables did not reveal a mediation effect (the paths models for all nonsignificant variables are detailed in Supplemental Figures A.2–A.5). For QoL, we found a significant *a path* (effect of intervention on QoL: −0.309*), a significant *b path* (effect of QoL on depression symptom severity: 0.757**), and a significant *c path* (total effect of intervention on depression symptom severity: −0.234*), as well as a significant indirect effect (effect of intervention on depression symptom severity, mediated by QoL: −0.234*). Additionally, a nonsignificant *c′ path* (direct effect of the intervention on depression symptom severity: −0.101) implied full mediation in that QoL at the end of the intervention (T1) statistically accounts for the relationship between intervention and depression symptom severity at 6 months follow-up (T2; Figure 1). Furthermore, the causal direction of the mediation effect of QoL can be inferred, as the mediation model implying the opposite direction of the mediation effect is not supported with our data; the Pearson correlation of group and QoL at T2 is not significant ($r = -.11$, $p = .0934$), indicating that there are no differences between intervention group and control group in QoL at 6 months follow-up (T2).

In order to further determine the specific mediating role of the facets of QoL, we also evaluated the potential mediating effects of the six dimensions of the AQoL-6D instrument distinctly (i.e., independent living, mental health, coping, relationships, pain, and senses). At it, only the subscales mental health (indirect effect: −0.282*) and coping (indirect effect: −0.249*) revealed significant mediation effects (for further details, see Supplemental Table A.1).

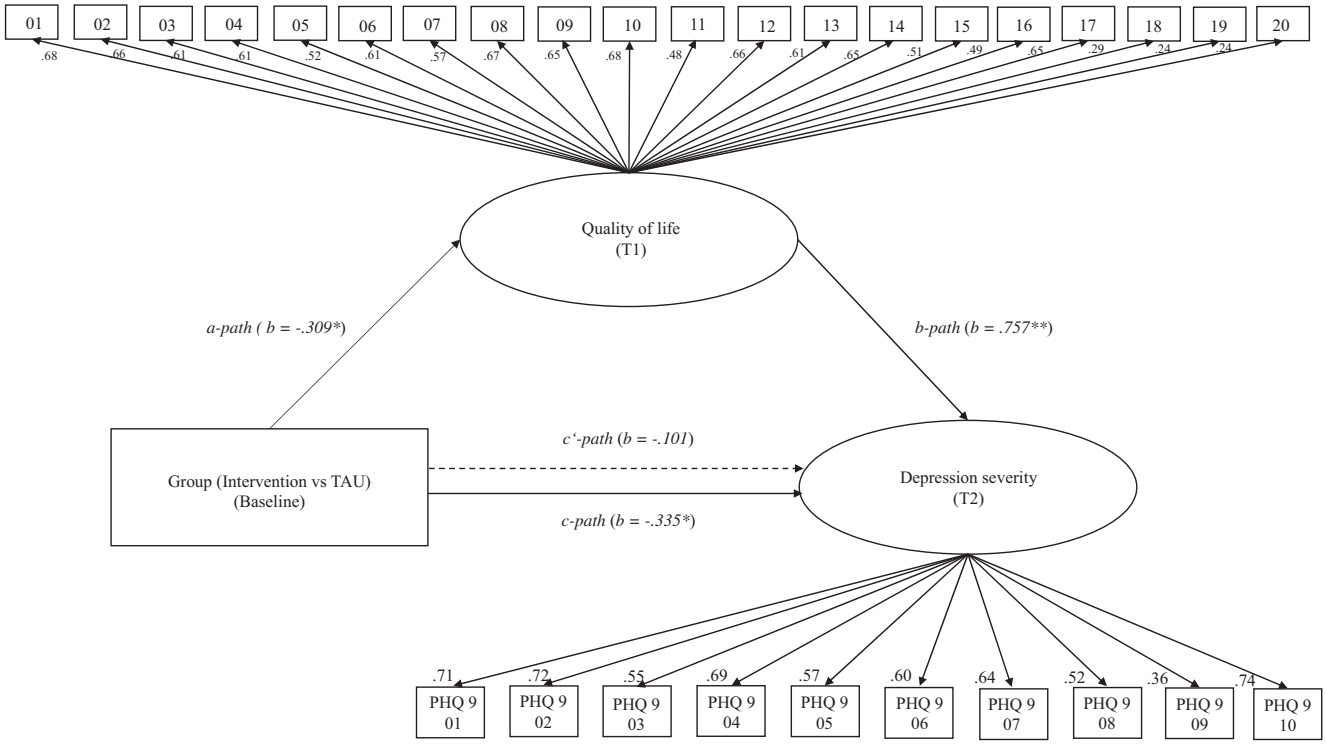
Table 3
Results of the Mediation Analyses

Mediator	A path	B path	Direct effect c'	Indirect effect ($a \times b$)	Total effect c ($a \times b + c'$)	RMSEA	SRMR
Pain intensity	−0.286	0.813**	−1.058*	−0.232	−1.290*	—[a]	—[a]
Pain-related disability	−0.236	0.560**	−0.199	−0.132	−0.331*	.044	.069
Pain self-efficacy	0.252	−0.573**	−0.187	−0.145	−0.332*	.051	.067
Quality of life	−0.309*	0.757**	−0.101	−0.234*	−0.335*	.057	.082
Work capacity	0.052	1.257**	−1.324*	0.065	−1.259*	—[a]	—[a]

Note. PHQ = Patient Health Questionnaire; RMSEA = root-mean-square error of approximation; SRMR = standardized root-mean-square residual. On the basis of modification indices, the following covariances were included in the mediation models, which were equal in all mediation models: group was allowed to covary with the mediator at T2 and the outcome at T1. The mediator at T1 was allowed to covary with the mediator at T2 and the outcome at T1. The mediator at T2 was allowed to covary with the outcome at T2. The outcome at T1 was allowed to covary with the outcome at T2. After this correction, the models were saturated. Scores represent standardized β coefficient based on modeling. The outcome was PHQ-9 depression symptom severity for all mediators.
[a] Because pain intensity and work capacity were manifest variables, no measurement model was estimated.
* $p < .05$. ** $p < .001$.

Figure 1

Path Model for Quality of Life



Note. Dotted lines represent nonsignificant paths; ellipses are latent variables, rectangles are manifest variables; factor loadings are standardized. PHQ = Patient Health Questionnaire; TAU = treatment-as-usual.
$^{*}p < .05$. $^{**}p < .001$.

Discussion

To the best of our knowledge, this study is the first to explore the mediators and mechanisms of change in a digital intervention to prevent depression in patients with CBP. With this secondary analysis of a large multicenter RCT of 295 participants conducted in routine health care settings (Sander et al., 2020), we found a full significant mediation of the intervention effects in preventing depressive symptom deterioration by QoL, as well as mediation effects of the subscales mental health and coping. All other potential intervening variables—specifically pain intensity, pain-related disability, pain self-efficacy, and work capacity—did not yield significant mediation effects.

These findings emphasize the importance of QoL and active coping in the curative process of patients with CBP in general and for the prevention of depression in this burdened population in particular. Hereby, the domain of active coping might be especially relevant, pointing to a genuine change mechanism in contrast to the rather spurious and tautological significance of the mental health subscale that possesses a high overlap with depression symptoms. These findings emphasize the importance to critically look at the actual operationalization of the potential mediators and outcomes and consider the concrete assessment instruments on the item- and subscale-level, differentiating between conceptually meaningful mediators and variables that capture merely symptoms. The results on active coping highlight the relevance of the self-management part of digital CBT and align well with the literature on this mediator in psychological interventions for depression (Bakker et al., 2018) and mental health in general (Domhardt et al., 2015; Groth et al., 2019). Additionally, in view of the specific operationalization of the coping subscale of the AQoL-6D (i.e., "How often do you feel in control of your life?"; "How much do you feel you can cope with life's problems?"), our findings also suggest to consider personal control and mastery as potential mechanisms of change in depression prevention in patients with CBP, which were found to be significant mediators of preventing depression in cancer survivors (Willems et al., 2017) and community samples before (Warmerdam et al., 2010).

Since we adhered to several quality criteria for process research (research design with RCT, control group, testing for multiple theoretically derived mediators, and temporal precedence) and had a sample size with adequate statistical power to detect small effects, the results seem robust and contribute to empirically supported information on change mechanisms in depression prevention, which were fundamentally lacking so far (Ebert et al., 2017; Moreno-Peral et al., 2020). The robustness of our findings might also apply for the nonsignificant results for the other putative mediator variables. However, the nonsignificant results on (pain) self-efficacy are in sharp contrast to the otherwise well-established importance of self-efficacy in psychological interventions for depression (Domhardt, Steubl, et al., 2021; Lemmens et al., 2016; Moreno-Peral et al., 2020). Furthermore,

theoretical assumptions and initial empirical findings suggest a relevant role of other mediators in the prevention of depression in patients with chronic pain, such as functional cognitions (Feldmann et al., 2021), catastrophizing (which may be inversely associated with self-efficacy; Edwards et al., 2016; Linton & Bergbom, 2011), or psychological flexibility (Lin et al., 2018). As of yet, the results of the present study imply to integrate intervention components that aim to improve the QoL and coping strategies of patients with CBP, in order to prevent depression symptom deterioration and depression onset in these individuals.

Strengths and Limitations

The present mediation study features several strengths, such as a high methodological rigor, adherence to quality criteria for process research, a large sample size, as well as the embeddedness into routine health care settings with high external validity (Sander et al., 2020). However, the findings of this study should be interpreted carefully, because of several limitations. First, as innate impediment in all mediation studies, we cannot rule out that the mediation effect of QoL and its subscales might have been actually due to other proxy variables (Cuijpers et al., 2019; Kazdin, 2007). Second, masking of participants in regard to their randomized group was not feasible, which is a common and hardly solvable potential bias in trials of psychological interventions (Domhardt et al., 2020; Munder & Barth, 2018). Third, because the control condition of TAU was not restricted to a certain treatment regime, differences in interventions and heterogeneous treatment dosages might have influenced the results. Yet, the randomization process was stratified for the recruiting clinics and we did not detect differences in health care utilization between the intervention and control group (Sander et al., 2020). Fourth, the findings of this study are limited to patients with CBP and might not generalize to other populations with depression. Finally, the results apply for interventions that are based on CBT in specific. Nevertheless, future studies might reveal that QoL and especially active coping are also relevant mediators of (digital) interventions that are built on other counseling theories next to CBT, such as interpersonal, psychodynamic, or client-centered approaches. Besides, these studies might contribute to the debate about the relative importance of common and specific factors (Cuijpers et al., 2019; Mulder et al., 2017) and could inform recent developments toward a process-based approach to psychotherapy (Hayes et al., 2020, 2022; Hofmann & Hayes, 2019).

Future Research

Forthcoming mediation studies should reveal whether the nonsignificant findings in the present study might be due to the operationalization and assessment of these constructs or hold constant in the endeavor to empirically establish the mediators and mechanisms of change in digital depression prevention for patients with chronic pain. Furthermore, although we evaluated a range of competing variables as potential mediators, other mediators such as cognitive distortions, reappraisal, acceptance, social engagement, reward responsiveness, quality of sleep, emotion regulation skills, as well as amount of behavioral activation or physical activity would have been of interest and should be explored in future studies. These forthcoming studies should also make the most out of the new opportunities of a digitalized process research approach, relying on smart sensing or passive data tracking, for example, in regard to mediators associated with behavioral activation or communication characteristics (Domhardt, Cuijpers, et al., 2021). Moreover, these studies should carefully consider the timing of the measurements of mediators and outcomes. Because rapid and initial symptom reductions can impede the detection of mediation effects that happen early in treatment, in case the assessments are scheduled to late (Domhardt, Steubl, et al., 2021). This might have occurred in the current trial, with a rather late first assessment of the potential mediators and outcomes at 9 weeks after baseline. Therefore, we recommend earlier assessments of mediators and outcomes to enable the detection of early intervening variable effects. Next to measurements early in treatment, fine-grained temporal designs would be of particular importance to bring the field another step forward. Empirically based information on the differential strengths of mediating effects as well as possible interactions between mediators and baseline characteristics (i.e., moderated mediation) might yield important insights for the advancement of psychological interventions and the personalization of depression treatment (Ebert & Cuijpers, 2018; Huibers et al., 2021). At this, novel opportunities in evidence synthesis associated with individual participant data meta-analysis (IPD-MA) might contribute to amend common limitations of process research (Domhardt et al., 2022). Probably the most important advantage over single mediational studies and conventional meta-analyses of aggregated data is the increase in statistical power, since IPD-MA combine the data from relevant trials on the individual participant level. Furthermore, IPD-MA allow for the consistent harmonization of variables (e.g., mediator and outcome instruments; measurement points) and standardization of imputation strategies across studies (Büscher et al., 2020, 2022; Domhardt et al., 2022; Lin et al., 2019). Overall, IPD-MA facilitate advanced statistical approaches for mediation analysis and might enable integrative and original findings on change mechanisms in psychological interventions for depression in the future.

In conclusion, the findings of this mediation study suggest an important role of QoL and active coping as change mechanism in digital interventions for the prevention of depression in patients with CBP; all other evaluated potential intervening variables were not significant in transmitting the interventions' effectiveness. This information is relevant for the empirically supported advancement of digital interventions, striving for enhanced programs with stronger effect sizes and better outcomes. Nevertheless, forthcoming research is needed to comprehensively extend and specify our understandings of the essential mediators and actual mechanisms of change in digital interventions for the prevention of depression.

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Chapter 9

Mechanisms of Change in Digital Health Interventions for Mental Disorders in Youth: Systematic Review

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Review

Mechanisms of Change in Digital Health Interventions for Mental Disorders in Youth: Systematic Review

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Abstract

Background: Digital health interventions (DHIs) are efficacious for several mental disorders in youth; however, integrated, evidence-based knowledge about the mechanisms of change in these interventions is lacking.

Objective: This systematic review aims to comprehensively evaluate studies on mediators and mechanisms of change in different DHIs for common mental disorders in children and adolescents.

Methods: A systematic literature search of the electronic databases Cochrane Central Register of Controlled Trials, Embase, MEDLINE, and PsycINFO was conducted, complemented by backward and forward searches. Two independent reviewers selected studies for inclusion, extracted the data, and rated the methodological quality of eligible studies (ie, risk of bias and 8 quality criteria for process research).

Results: A total of 25 studies that have evaluated 39 potential mediators were included in this review. Cognitive mediators were the largest group of examined intervening variables, followed by a broad range of emotional and affective, interpersonal, parenting behavior, and other mediators. The mediator categories with the highest percentages of significant intervening variables were the groups of affective mediators (4/4, 100%) and combined cognitive mediators (13/19, 68%). Although more than three-quarters of the eligible studies met 5 or more quality criteria, causal conclusions have been widely precluded.

Conclusions: The findings of this review might guide the empirically informed advancement of DHIs, contributing to improved intervention outcomes, and the discussion of methodological recommendations for process research might facilitate mediation studies with more pertinent designs, allowing for conclusions with higher causal certainty in the future.

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KEYWORDS

children and adolescents; mental disorders; mediator; mechanisms of change; digital health intervention; psychotherapy; mobile phone

Introduction

Background

Mental disorders in children and adolescents are common, with prevalence rates ranging from 10% to 20% worldwide [1]. These disorders contribute substantially to the global burden of disease in youth [2], and about half of all mental disorders across the life span have their onset in adolescence [3]. Hence, early psychotherapeutic interventions are essential to counteract the risk of chronification and prevent possible negative long-term effects [1]. However, a substantial proportion of children and adolescents with mental disorders do not receive adequate psychotherapeutic or psychosocial care [4-6] owing to different

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individual and structural barriers to treatment uptake [7]. Furthermore, the availability of mental health care is often insufficient to adequately meet treatment demands, particularly in rural regions [8] and low-income countries [9].

Digital health interventions (DHIs), such as internet- and mobile-based interventions with a psychotherapeutic focus (DHI_{PSY}), offer the possibility of addressing some barriers to treatment uptake and might contribute to extending mental health care, given their various presumed advantages, such as possible cost- and time-efficient use, independence from spatial and temporal circumstances, potential anonymity, high degrees of flexibility, and autonomy for users. These assets may be especially important during the COVID-19 pandemic and allow for continued mental health care despite contact restrictions and physical distancing [10]. Furthermore, in view of the fact that youth are particular familiar with digital devices (so-called *digital natives*; Children in a digital world [11]), the use of DHIs might be especially appealing to this younger age group [12]. DHIs can be distinguished and characterized based on their theoretical basis, the type of technical implementation, the area of application, and the extent of accompanying human support [13,14]. The type and the intensity of *guidance* in DHIs can vary on the continuum from (1) pure self-help interventions without any human support (so-called *unguided interventions*) to (2) interventions with some support (*guided interventions*), to (3) videoconference-based psychotherapy with the internet as the sole communication medium between therapists and patients [15].

The efficacy of DHI_{PSY} for some common mental disorders in children and adolescents has been established using meta-analyses [12,16-19]. For example, Vigerland et al [19] evaluated the efficacy of internet-based cognitive behavioral therapy for a range of mental disorders, including anxiety, depression, behavioral problems, obsessive-compulsive disorder, and some somatic disorders such as chronic pain and insomnia. This meta-analysis revealed a moderate, aggregated effect size favoring internet-based cognitive behavioral therapy over waitlist (g=0.62, 95% CI 0.41-0.84; P<.001). In contrast, Hollis et al [20] appraised the evidence on the efficacy of DHI_{PSY} for other mental disorders, including attention-deficit/hyperactivity disorder, autism, psychotic disorders, and eating disorders in their review as uncertain and necessitating future research regarding moderators of intervention effects. Current empirical knowledge suggests that older children and adolescents benefit more from DHI_{PSY} than younger children [12,20]. In addition, the well-established finding that guided interventions are more efficacious than unguided interventions in adults [21,22] also seems to apply for DHI_{PSY} in youth [12,20]. Complementing the evidence base and representing another major area of application, DHIs with a focus on health promotion (DHI_{HP}), for example, on alcohol consumption or other lifestyle and health behaviors, revealed a considerably smaller effect size (Cohen d=0.14, 95% CI 0.00-0.27) [23] when compared with DHI_{PSY} with a genuine psychotherapeutic foundation such as cognitive behavioral therapy (g=0.72, 95% CI 0.55-0.90; P<.001) [16].

Given this rather heterogeneous body of research regarding the efficacy and effectiveness of DHIs, comprising various interventions with different theoretical orientations, foci, and delivery modes, for mental health issues in children and adolescents, it seems both timely and worthwhile to investigate the presumed working mechanisms in these technology-delivered interventions. This is because evidence-based knowledge on the mediators and mechanisms of change (specific for different approaches of DHI_{PSY} and DHI_{HP}) can inform intervention development and mental health care practices, illustrating pathways to more powerful intervention packages and improved outcomes [24-26]. The first step in understanding the underlying processes in DHIs is to analyze the mediators. A mediator is an intervening variable that can explain the statistical relationship between an independent variable (eg, a DHI) and a dependent variable (eg, a symptom change) [25], and can thereby potentially point to a mechanism through which an intervention achieves its effects. Although various methods for statistical mediation analysis are available (eg, MacKinnon et al [27]), comprising different approaches such as latent growth curve modeling [28] or structural equation modeling [29], the seminal approach of Baron and Kenny [30] is still one of the most applied procedures to evaluate the intervening variable effect of a potential mediator, despite having received criticism with regard to some limitations, such as low statistical power, difficulties in the assessment of multiple mediators, or quantification of the mediation effect magnitude [24]. Although statistical mediation may be established either with the so-called causal-steps approach by Baron and Kenny [30] or by more recent methods correcting some of its limitations (eg, Kraemer et al [31]), it is important to consider that mediators might be identical to a mechanism of change (ie, the actual process responsible for change), but might also be a proxy for 1 or more other variables that do not explain the hypothesized mechanism [25]. Thus, to determine the degree of validity that a mediator is actually representative of for being considered a true change mechanism, Kazdin proposed several quality criteria for psychotherapy process research [25] that can be consulted when assessing the scope and justification of causal inferences: (1) Strong association (among treatment, mediator, and outcome), (2) specificity (a mediator accounts for the indirect effect of treatment on outcome), (3) consistency (the association must be replicable), (4) experimental manipulation (use of either a randomized controlled trial [RCT] design where the intervention variable is manipulated or an experimental design where the mediator itself is directly manipulated), (5) timeline or temporality (the intervention must lead to changes in the mediator, which must temporally precede changes in the outcome), (6) gradient (ie, a dose-response relationship: greater activation of the mediator is associated with greater change in the outcome), and (7) plausibility or coherence (the proposed mediator must be embedded in a plausible theoretical framework).

The evidence base for the mediators and mechanisms of change in conventional face-to-face psychotherapies for children and adolescents is scarce, and only a few studies have been designed to investigate the therapeutic processes in these interventions

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[32]. For example, 2 systematic reviews dedicated to evaluating the mechanisms of change found that only a small number of eligible primary studies actually conducted mediation analyses, with only 9% (6/67) [33] and 17% (8/46) of included clinical trials [34] attempting to evaluate mediation effects. In addition, Schmidt and Schimmelmann [35] reviewed the empirical literature on mediators in psychotherapeutic interventions for common mental disorders in youth and concluded that most eligible studies evaluated mediators referring to the parent-child interaction (eg, family cohesion and parental support), next to mediators within the patient (eg, self-efficacy, motivation, coping, interpersonal skills, as well as changes in dysfunctional cognitions and negative emotions) and characteristics of the intervention (eg, duration of treatment, number of patient-therapist contacts, and application of specific intervention techniques). The included studies revealed inconsistent patterns of mediation effects related to therapist factors, such as flexibility, adherence to treatment, or therapeutic alliance [35]. Moreover, as central conceptual and methodological requirements for mediation analyses were often not met by studies in this review, causal inferences were widely precluded, necessitating future process research with higher methodological rigor [35].

Objectives

Although research on DHIs is a fast growing field [36] and might also offer intriguing opportunities for psychotherapeutic process research [24,37], we are not aware of any systematic review of the mediators and mechanisms of change in DHI_{PSY} and DHI_{HP} for common mental disorders in youth published to this point. Therefore, this study aimed to: (1) systematically review the current state of research on mediators and mechanisms of change in various DHIs for mental disorders in children and adolescents, (2) identify mediators and potential mechanisms of change in these interventions, and (3) evaluate the methodological quality of eligible mediation studies according to the quality criteria for process research mentioned above.

Methods

This systematic review was reported in accordance with the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines [38] and was a priori registered with the Open Science Framework [39].

Eligibility Criteria

Studies were eligible for inclusion if they fulfilled the following criteria: (1) participants were children (0-13 years) or adolescents (14-21 years) diagnosed with a mental disorder or exhibited clinically relevant symptoms of a mental disorder; (2) in the case of mixed samples with adolescents and young adults, the mean age of the sample was not above 21 years; (3) the interventions were designed for children or adolescents, or for parents of children or adolescents fulfilling the first criterion; (4) the diagnosis of mental disorders was based on the diagnostic and statistical manual of mental disorders, or the International Classification of Diseases criteria and was assessed with a validated and standardized clinical interview, or a standardized self-report instrument, or standardized ratings by significant others (eg, parents, teachers, clinicians); (5) samples of mixed or comorbid mental disorders were included; (6) studies with different recruitment strategies were eligible; (7) interventions with different theoretical orientations were eligible; (8) the intervention was predominantly delivered through the internet (eg, via web browsers or mobile or smartphone apps); (9) interventions with different degrees of human guidance and completely self-guided interventions were eligible for inclusion; (10) different active and passive control groups (CGs) were included; (11) changes in the symptoms and (12) mediators were reported; (13) at least one mediation analysis was performed; (14) studies were RCTs or secondary analyses of RCTs published in a peer reviewed journal in English language.

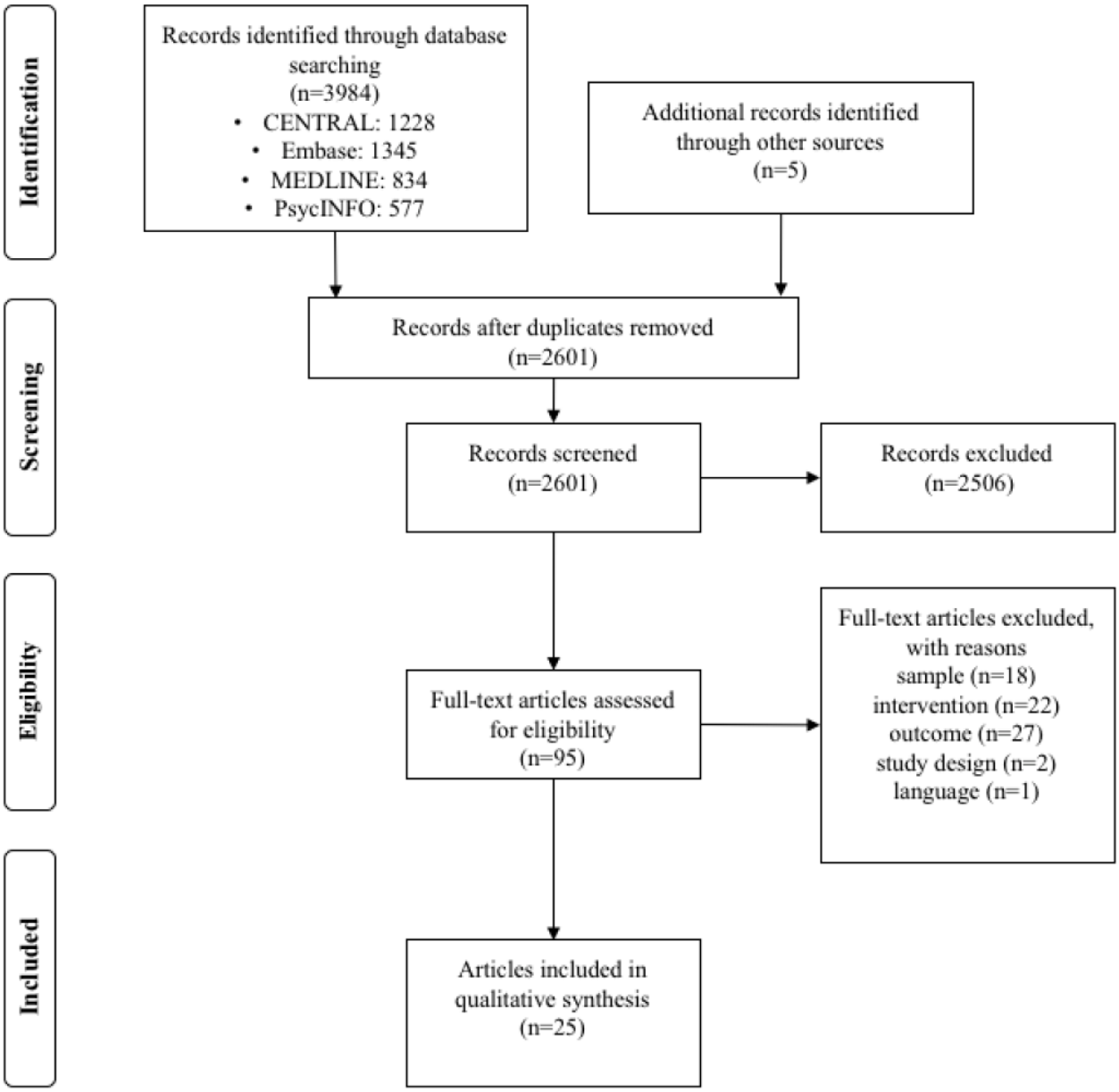
Systematic Literature Search and Study Selection

The search strategy was 3-fold. First, systematic literature searches were conducted in the Cochrane Central Register of Controlled Trials, Embase, MEDLINE (ie, Ovid MEDLINE, Ovid MEDLINE Epub Ahead of Print, Ovid MEDLINE In-Process and Other Non-Indexed Citations, Ovid MEDLINE Daily Update), and PsycINFO databases from database inception until May 30, 2020. The search strings were built on established prior search strings [24,40] further adapted to specifically meet the research questions at hand and modified for each database in Ovid (for details on all search strings, see Multimedia Appendix 1). Second, the reference lists of all eligible studies and other relevant reviews were manually searched to identify further studies that met our inclusion criteria (ie, backward searches). Third, a citation-search (ie, forward search) was conducted in the Web of Science database.

Study selection was conducted with the support of a software tool for systematic reviews [41]. Duplicates were detected automatically by the software or were manually removed. First, 1 reviewer (SE) screened titles and abstracts of all the remaining studies and discarded irrelevant articles. Second, the full texts of all potentially relevant articles were screened in terms of the aforementioned eligibility criteria independently by 2 reviewers (SE and HN). Disagreements were resolved by consultation with a third reviewer (MD). The full process of the systematic literature search and study selection is displayed in the PRISMA flowchart of Figure 1.

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Figure 1. PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) flowchart.



Data Extraction

Two independent reviewers (SE and HN) extracted the following data: study information items (name of first author, country, and year), sample information (sample size and age), intervention characteristics (theoretical orientation, number of modules, and duration of intervention), information about control conditions, and information about outcomes (mediator type, instrument, and statistical analysis of mediation). Authors were contacted via email in case of missing information essential for decisions on study selection and the application of the systematic review.

Categorization of Studies

The included studies were divided into 2 categories: studies evaluating interventions with a psychotherapeutic focus (ie, DHI_{PSY}) and studies evaluating interventions with a focus on health promotion (comprising interventions targeting health behavior, lifestyle, and behavior change interventions for the purpose of primary and secondary prevention; ie, DHI_{HP}). Of note, interventions with rehabilitation or tertiary prevention focus were not included.

Quality Assessment

Risk-of-Bias Assessment

The methodological quality of the included studies was assessed independently by 2 reviewers (SE and HN) using the Cochrane risk-of-bias (RoB) tool for randomized trials (version 2, RoB2; [42]) on 5 domains: (1) bias arising from the randomization process, (2) bias due to deviations from intended interventions, (3) bias due to missing outcome data, (4) bias in measurement of the outcomes, and (5) bias in selection of the reported result. The included studies were rated as having *low*, *unclear*, or *high RoB* in each domain [42]. Interrater reliability was calculated using the Cohen κ in RStudio (version 1.2.1335; [43]).

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Quality Criteria for Process Research and Approximating Causality

The included studies were rated by 2 independent reviewers (SE and HN). The rating system was based on Kazdin's [25] initial criteria to approach causality, modified by Domhardt et al [24] and Lemmens et al [44]. To meet the respective criteria, studies had to: (1) use an appropriate RCT design, (2) include a CG, (3) report a theoretical foundation for mediators, (4) have a minimum sample size of 40 participants per group, (5) examine multiple mediators within 1 study, (6) assess temporality (3 or more assessments of the mediator variables and outcomes), (7) experimentally manipulate the mediator, and (8) reveal a strong statistical association among intervention, mediator, and outcome (operationalized as statistical significance of $P<.05$, as suggested by Moreno-Peral et al [45]). All criteria were rated as fulfilled or not fulfilled. In accordance with prior research [24,44], criteria specificity, consistency, and gradient were not assessed, as they are not meaningfully applicable in single studies (consistency) or are too exclusive for some therapeutic processes (gradient and specificity).

Results

Study Characteristics

Altogether, data from 25 (k=25) publications were analyzed [46-70]. Specifically, 52% (13/25) of the studies [46,47,49,54,56,58-60,64-67,69] evaluated DHI_{PSY} and 48% (12/25) of the studies evaluated DHI_{HP} [48,50-53,55,57,61-63,68,70]. In the studies, a total of 4884 participants were randomized. Studies on DHI_{PSY} accounted for 43.2% (2110/4884) of participants, and studies on DHI_{HP} accounted for 56.8% (2774/4884) of participants. The overall sample sizes varied from 51 [59] to 818 [63]. The median publication year was 2014 (2002 [48] to 2020 [49]). Most studies were conducted in the United States (17/25, 68%), and most of the study participants were female (2985/4884, 61.18%). In 1 study, no information was provided regarding the distribution of sex [54]. The mean age of participants was 18.49 (SD 2.01) years. The lowest mean age was 5.4 (SD 2.2) years [67], and the highest was 21.02 (SD 2.16) years [70]. Participants were younger in studies evaluating DHI_{PSY} compared with participants in studies evaluating DHI_{HP} (17.11 vs 19.67 years). The exact information on the average age of the final sample was not provided in 4 studies [54,56,63,68]. Most interventions took place without parental involvement and were directed at the youth themselves (20/25, 80%). In 20% (5/25) of the studies, interventions for children [54,67] as well as interventions for both children and adolescents [46,65] and for adolescents only [64] were evaluated with the involvement of parents (including intervention components for parents or parent training). Demographic information about the parents who participated was provided in 16% (4/25) of the studies [46,54,65,67]. Study participants were recruited predominantly from educational or health-related settings (15/25, 60%). In 32% (8/25) of the studies, participants were made aware of the study through both web-based advertising (including social media and websites) and conventional advertising (including letters and flyers). To identify potential participants, one study (1/25, 4%) used data from a mass web-based survey [59]. Information on recruitment strategy could not be identified in 4% (1/25) of the studies [68]. Across studies, the average study dropout rate accounted for 18% (range 0% [62] to 39.3% [54]). In 4% (1/25) of the studies, the dropout rate was not reported [46].

The interventions were directed toward a broad range of mental health problems, including risky drinking behavior (including risky or heavy drinking and binge drinking; 11/25, 44%), depressive disorders (5/25, 20%), anxiety disorders (including separation anxiety, generalized anxiety disorder, social phobia, and specific phobia; 3/25, 12%), behavioral problems (2/25, 8%), and insomnia (1/25, 4%). Furthermore, 12% (3/25) of the studies evaluated interventions that addressed multiple disorders simultaneously (ie, transdiagnostic interventions). De Bruin et al [47] addressed transdiagnostic *psychopathological abnormalities* (including affective, anxiety, and somatic problems; problems concerning attention-deficit/hyperactivity disorder; oppositional defiant behavior; and conduct problems). Levin et al [60] addressed *psychological problems* such as depressive disorders, generalized anxiety disorder, social phobia, alcohol consumption, academic worries, worries concerning eating, hostility, and negative stress. Another intervention addressed depression, anxiety, and stress [56]. Of note, there were 2 interventions evaluated and applied in more than 1 study (the *e-CHUG* interventions in 4 studies; and the *BRAVE* interventions in 2 studies), but the investigated mediators differed in all studies; thus, these publications were regarded as distinct entities and single studies (see Multimedia Appendix 2 [46-70] for details).

Internet-based interventions were evaluated in 92% (12/13) of the studies on DHI_{PSY}. Most interventions were based on the components of cognitive behavioral therapy [46,47,49,59,66]. In addition, relaxation strategies, such as progressive muscle relaxation and autogenic training [49], and elements of social learning theory [54] were deployed. Further interventions were based on the acceptance and commitment therapy [60], components of systemic family therapy, problem solving and communication training, cognitive restructuring, and alternative family roles [64]. One intervention [56] was based on the *temporal model of control*. In 23% (3/13) of the studies, precise information on the theoretical orientation and background of the intervention was not available [58,67,69]. Moreover, 7% (1/13) of the studies evaluated a mobile-based intervention based on a self-monitoring program [58].

All DHI_{HP} studies were internet-based and included a feedback component (12/12, 100%). The so-called *e-CHUG* tool was evaluated in 33% (4/12) of the studies [51,57,62,68]. Feedback was provided via email [48,53] or in person using a motivational interviewing approach [51,52]. In addition to the feedback components, cognitive components such as expressive writing [70] and retrieval of remembered information from feedback were evaluated [57]. A detailed overview of the study characteristics is provided in Multimedia Appendix 2.

Mediators

An overview of the classification of mediators and their empirical support is provided in Table 1. A total of 39 potential

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mediators were investigated in the included RCTs. Among these, more than half of the mediators were evaluated as significant (21/39, 54%). With 48% (19/39) intervening variables, the largest group of all examined intervening variables was of a cognitive nature. A total of 13 cognitive mediators were evaluated as significant in the primary studies (13/19, 68%). We further divided the group of cognitive mediators into the *assessment* (examined: 8/39, 20%; significant: 5/8), *motivation* (examined: 1/39, 2%; significant: 0/1, 0%) and *cognitive processes* subcategories (examined: 10/39, 25%; significant: 8/10, 80%). Further evenly investigated mediator categories were emotional/affective (examined: 4/39, 10%; significant: 4/4, 100%), interpersonal (examined: 4/39, 10%; significant: 1/4, 25%), and parenting behavior mediators (examined: 4/39, 10%; significant: 0/4, 0%). The second largest group of mediators was not clearly classifiable into one of the aforementioned categories and was thus subsumed into a separate *other* mediator category (examined: 8/39, 20%; significant: 3/8, 38%). Of note, a Wilcoxon rank-sum test revealed no difference in the sample sizes between studies that found at least one significant mediator and studies that found no significant mediator (W {19,6}=59; *P*=.93).

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Table 1. Classification of mediators.

Mediators	Studies, n (%) (n=25)	Age (years), range[a]	Guidance	Disorder	Effect size[b]	Significance	Criteria met ≥5
Emotional and affective mediators							
Emotional self-perception	1 (4)	14-22	Unguided	Depression	Partially standardized ES[c]=−1.049 (95% CI −1.35 to −0.755)	Yes	(+)[d]
Fear	1 (4)	16-24	Internet-based psychotherapy	Depression	Between groups ES=0.49 (95% CI 0.24 to 0.75)	Yes	(+)
Hopelessness	1 (4)	>18	Unguided	Depression	Cohen *d*=1.13 (between groups follow-up)	Yes	(+)
Thought-related distress	1 (4)	Undergraduate students	Guided self-help	Generalized anxiety disorder	Cohen *d*=0.526 (between groups follow-up)	Yes	(+)
Interpersonal mediators							
Parent-Youth conflict	1 (4)	12-19	Internet-based psychotherapy	Depression	—[e]	Yes	(+)
Family conflicts related to diabetes management	1 (4)	12-19	Internet-based psychotherapy	Depression	—	No	(+)
Failed help or negative social support	1 (4)	12-19	Internet-based psychotherapy	Depression	—	No	(+)
Social skills	1 (4)	8-17	Guided self-help	Social phobia	—	No	(+)
Parenting behavior mediators							
Appropriate education	1 (4)	10-13	Guided self-help	Behavioral problems	—	No	(+)
Skill in setting clear boundaries	1 (4)	10-13	Guided self-help	Behavioral problems	—	No	(+)
Severity and inconsistent education	1 (4)	10-13	Guided self-help	Behavioral problems	—	No	(+)
Change in parenting behavior	1 (4)	3-9	Guided self-help	Behavioral problems	—	No	(−)[f]
Cognitive mediators							
Assessment							
Assessment of discrepancy[g]	2[g] (8)	College students; College students	Guided self-help; guided self-help	Risky drinking behavior	—; —	No	(+)
Assessment of peer drinking behavior[g]	2[g] (8)	18-24; 18-24	Guided self-help; guided self-help	Risky drinking behavior	—; —	Yes	Different result

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Mediators	Studies, n (%) (n=25)	Age (years), range[a]	Guidance	Disorder	Effect size[b]	Significance	Criteria met ≥5
Perceived norm[g]	4[g] (16)	18-25; Students; First semester students; 18-26	Guided self-help; unguided; guided self-help; unguided	Risky drinking behavior	—; Cohen *d*=−0.2 (ES Biannual); —; —	Different results[h]	(+)
Motivation							
Motivation to change drinking behavior	1 (4)	College students	Unguided	Risky drinking behavior	—	No	(+)
Cognitive processes							
Alcohol-related expectations	—	Students	Guided self-help	Risky drinking behavior	—	Yes	(+)
Remembered information	1 (4)	Students	Guided self-help	Risky drinking behavior	—	Yes	(+)
Mastering	1 (4)	16-25	Internet-based psychotherapy	Depression	Between groups ES=0.94 (95% CI 0.64 to 1.23)	Yes	(+)
Willingness to cope	—	Students	Unguided	Depression	—	No	(−)
Cognitive arousal before falling asleep	1 (4)	Students	Unguided	Insomnia	—	No	(+)
Sleep-related cognition	—	Students	Unguided	Insomnia	—	Yes	(+)
Postevent processing	1 (4)	8-17	Guided self-help	Social phobia	—	Yes	(+)
Mindful acceptance	1 (4)	Students	Guided self-help	Transdiagnostic[i]	Proportion mediated ES=range 16.05% to 28.57%	Yes	(−)
Obstruction of appreciation of life	—	Students	Guided self-help	Transdiagnostic[i]	Proportion mediated ES=range 29.18% to 57.94%	Yes	(−)
Perceived control	1 (4)	18-21	Guided self-help	Transdiagnostic[i]	Cohen *d*=0.07; Cohen *d*=0.59; Cohen *d*=0.66 (between groups follow-up)	Yes	(+)
Other							
Alcohol consumption as coping behavior	1 (4)	18-21	Unguided	Risky drinking behavior	—	No	(+)
Therapy adherence	1 (4)	7-18	Guided self-help	Anxiety disorder	—	No	(−)
Eating disorder	1 (4)	18-25	Unguided	Depression	—	Yes	(+)

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Mediators	Studies, n (%) (n=25)	Age (years), range[a]	Guidance	Disorder	Effect size[b]	Significance	Criteria met ≥5
Overall sleep quality	1 (4)	Students	Unguided	Insomnia	—	No	(+)
Chronotypical	1 (4)	Students	Unguided	Insomnia	—	No	(+)
Physical arousal before falling asleep	1 (4)	Students	Unguided	Insomnia	—	Yes	(+)
Trauma-related sleeping disorder	1 (4)	Students	Unguided	Insomnia	—	No	(+)
Insomnia	1 (4)	12-19	Guided self-help	Transdiagnostic[i]	—	Yes	(+)

[a]If age range was not reported, participant group labels were used.

[b]Effect size measures differed across studies.

[c]ES: effect size

[d]Met 5 or more criteria.

[e]Not available.

[f]Met fewer than 5 criteria.

[g]If mediator was assessed in more than 1 study, data and results were separated with ";".

[h]The only mediator nonsex-specific perceived norm was not significant.

[i]Transdiagnostic intervention targets more than one disorder.

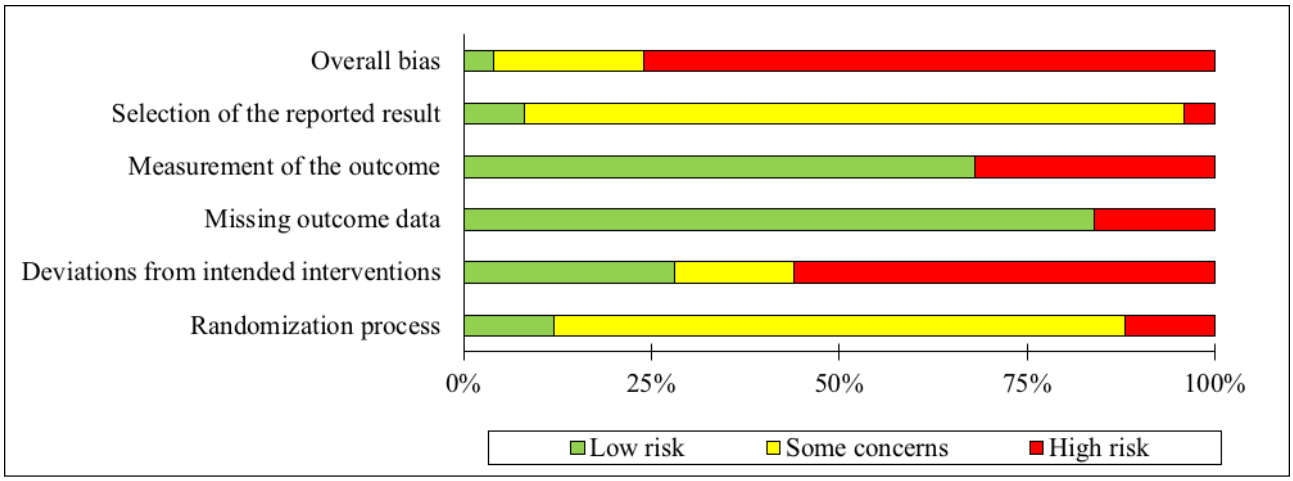
A broad range of different approaches to mediation analyses was deployed, with some studies relying on several strategies at once. Bootstrapping (eg, Preacher and Hayes [71]) was used in almost half of the studies (11/25, 44%). In 32% (8/25) of the studies, the mediation analysis was based on the approach of Baron and Kenny [30], and in addition, 8% (2/25) performed a Sobel test. Furthermore, 32% (8/25) of the mediation analyses were performed using structural equation modeling (7/25, 28% using the MPlus software). Moreover, 4% (1/25) of the studies performed multiple regression analysis according to the Judd and colleagues paradigm [72], and another study did not provide any information on the statistical analysis.

Quality Assessment of Included Studies

Risk-of-Bias Assessment

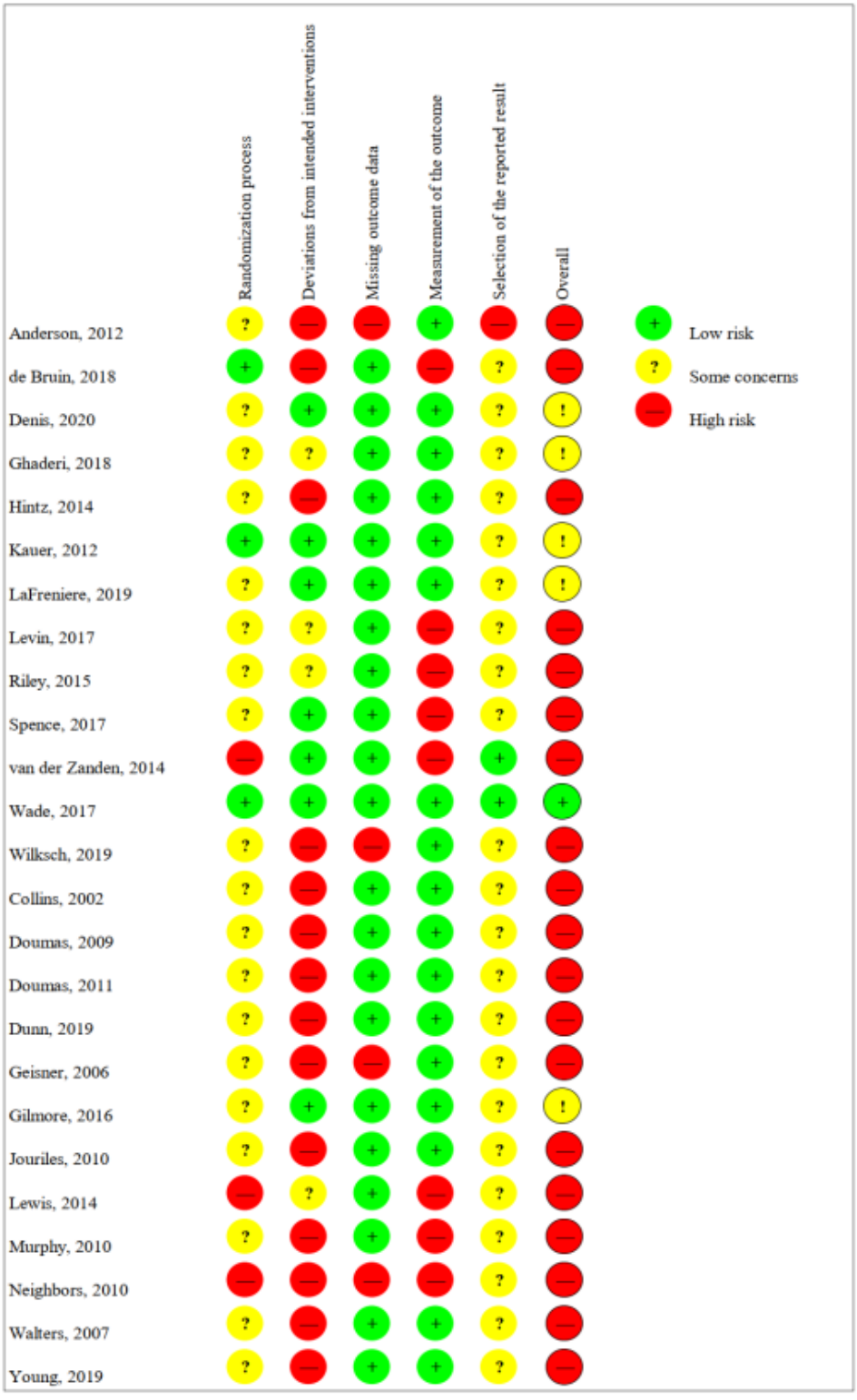
As illustrated in the *RoB2 Graph* (Figure 2), approximately three-quarters (19/25, 76%) of the included studies were rated as having a *high* RoB. In more than half of the studies (14/25, 56%), the *bias due to deviation from the intended intervention* was rated as *high*. The RoB on this domain was more often evaluated to be *high* in studies on DHI_{HP} (10/25, 40%) when compared with studies on DHI_{PSY} (4/25, 16%). Both the randomization procedure and the process of reporting results were predominantly rated with *some concern* across studies (19/25, 76% and 22/25, 88%). Interrater reliability varied across domains from Cohen κ=0.76 to Cohen κ=0.93. According to Landis and Koch [73], these agreements can be rated as *substantial* to *almost perfect*. A summary of the RoB2 assessments is shown in Figure 3.

Figure 2. Risk-of-bias graph.



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Figure 3. Risk-of-bias summary.



Evaluation of the Quality Criteria for Process Research and Approximating Causality

The evaluation of the included studies with regard to the methodological quality of process research revealed that in both the DHI_{PSY} and the DHI_{HP} groups, most studies (DHI_{PSY}: 9/13, 69% vs DHI_{HP}: 11/12, 92%) fulfilled 5 or more out of the 8 criteria. Owing to the eligibility criteria used in this review, almost all studies met the requirement of an RCT design (24/25, 96%) and a CG (24/25, 96%). In the publication by Anderson et al [46], the results from 8% (2/25) of the studies were jointly reported, with only the second study evaluating a DHI_{PSY} without a direct comparison with the CG, although this criterion was fulfilled in the first study. Even if mediators were collected at more than 2 measurement time points in more than half of the studies (15/25, 60%; including follow-up), an evaluation of the chronology of changes in the mediator variable or variables and outcomes was conducted in only 4% (1/25; de Bruin et al

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[47]) of the studies. Furthermore, 8% (2/25) of the studies, Hintz et al [56] and Jouriles et al [57] implemented direct experimental manipulation of mediators. A detailed overview of the evaluation of the methodological quality criteria for process research and the approximation of causality are outlined in Tables 2 and 3, as well as in Multimedia Appendix 3.

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Table 2. Quality criteria for process research and approximation of causality (n=25).

Studies	Randomized controlled trial	CG[a]	Theoretical foundation	n≥40 (Each CG and EG[b])	Various mediators	Time sequence	Manipulation	*P* value (<.05)[c]	Σ (Yes)
DHI_{PSY}[d]									
Anderson, 2012 [46][e]	No[f]	No	Yes[g]	No	No	No	No	Yes	2
de Bruin et al [47]	Yes	Yes	Yes	No	No	Yes	No	Yes	5
Denis et al [49]	Yes	Yes	No	Yes	Yes	No[h]	No	Yes	5
Ghaderi et al [54]	Yes	Yes	Yes[i]	Yes	Yes	No[h]	No	Yes	6
Hintz, 2014 [56]	Yes	Yes	Yes	Yes	No	No[h]	Yes	Yes	6
Kauer et al [58]	Yes	Yes	Yes	Yes	No	No[h]	No	Yes	5
LaFreniere, and Newman [59]	Yes	Yes	Yes	No	No	No[h]	No	Yes	4
Levin et al [60]	Yes	Yes	No	No	Yes	No	No	Yes	4
Riley et al [64]	Yes[j]	Yes[j]	Yes	Yes	Yes	No[h]	No	Yes	6
Spence et al [65]	Yes	Yes	Yes	No	Yes	No[h,k]	No	Yes	5
Zanden et al, 2014 [66]	Yes	Yes	Yes	Yes	Yes	No[h]	No	Yes	6
Wade et al [67]	Yes	Yes	Yes	No[i]	No	No[h]	No	Yes	4
Wilksch, O'Shea, and Wade [69]	Yes	Yes	Yes	Yes	No	No[h]	No	Yes	5
DHI_{HP}[l]									
Collins, Carey, and Sliwinski [48]	Yes	Yes	Yes	Yes	No	No[h]	No	Yes	5
Doumas, McKinley, and Book [50]	Yes	Yes	Yes	No	No	No	No	Yes	4
Doumas et al [51]	Yes	Yes	Yes	Yes	No	No	No	Yes	5
Dunn, 2019 [52]	Yes	Yes	Yes	Yes	No	No	No	Yes	5
Geisner, Neighbors, and Larimer [53]	Yes	Yes	Yes	Yes	Yes	No	No	Yes	6

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Studies	Randomized controlled trial	CG[a]	Theoretical foundation	n≥40 (Each CG and EG[b])	Various mediators	Time sequence	Manipulation	*P* value (<.05)[c]	∑ (Yes)
Gilmore and Bountress [55]	Yes	Yes	Yes	Yes	No	No	No	Yes	5
Jouriles et al [57]	Yes	Yes	Yes	No	No	No	Yes	Yes	5
Lewis et al [61]	Yes	Yes	Yes	Yes	No	No[h]	No	Yes	5
Murphy, 2010 [62][h]	Yes	Yes	Yes	Yes	Yes	No[h]	No	Yes	6
Neighbors et al [63]	Yes	Yes	Yes	Yes	Yes	No[h]	No	Yes	6
Walters, Vader, and Harris [68]	Yes	Yes	Yes	Yes[m]	No	No[h]	No	Yes	5
Young and Neighbors [70]	Yes	Yes	Yes	Yes	No	No	No	Yes	5

[a]CG: control group.

[b]EG: experimental group.

[c]Overall significance level *P*<.05; only data from study 2 taken into account.

[d]DHI_{PSY}: digital health interventions with a psychotherapeutic focus.

[e]Only data from study 2 are taken into account.

[f]*No* indicates criteria not met.

[g]*Yes* indicates criteria met.

[h]More than 2 measurements (including follow-up) reported, but no evaluation of time sequence.

[i]Subscales have no theoretical foundations.

[j]Initial study had a randomized controlled trial design; in secondary analysis, both groups were taken together.

[k]Due to missing follow-up data in the waitlist condition, mediation analysis was conducted only with data from baseline and after 12 weeks (at least 3 sessions were completed).

[l]DHI_{HP}: digital health interventions with a focus on health promotion.

[m]Information was given after contacting authors.

Table 3. Number of studies meeting each single quality criterion for process research (n=25).

Criterion	DHI_{PSY}[a], n (%)	DHI_{HP}[b], n (%)	Overall, n (%)
Randomized controlled trial	12 (48)	12 (48)	24 (96)
CG[c]	12 (48)	12 (48)	24 (96)
Theoretical foundation	11 (44)	12 (48)	23 (92)
n≥40 (for CG and EG[d] each)	7 (28)	10 (40)	17 (68)
Evaluation of various mediators	6 (24)	3 (12)	9 (36)
Time sequence or temporality	1 (4)	0 (0)	1 (4)
Manipulation of mediators	2 (8)	0 (0)	2 (8)
P<.05	13 (52)	12 (48)	25 (100)

[a]DHI_{PSY}: digital health interventions with a psychotherapeutic focus.

[b]DHI_{HP}: digital health interventions with a focus on health promotion.

[c]CG: control group.

[d]EG: experimental group.

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Discussion

Principal Findings

This systematic review, to the knowledge of the authors the first of its kind, comprehensively evaluated research on mediators and mechanisms of change in DHIs for common mental disorders in youth. Altogether, 25 studies were included in the review, that have examined 39 distinct mediators. Cognitive variables were found to be the most often investigated mediators, followed by a broad range of other mediators. Even though our eligibility criteria were not limited to a specific mental health condition in youth, only a rather low number of studies were identified by our systematic literature searches, a finding that corresponds to the limited evidence base of research on mechanisms of change in psychotherapy in general [37,74], and for children and adolescents in specific [24,35,37], necessitating further high-quality research efforts to improve interventions and mental health care practices for this younger age group.

Remarkably, our findings indicate that the mediator category with the highest percentage of significant intervening variables was the affective or emotional mediator group (4/4, 100%). The proportions of significance in other mediator categories were by far less high and included combined cognitive (13/19, 68%), other (3/8, 37%), interpersonal (1/4, 25%), and parenting behavior–related mediators (0/4, 0%). The consistent nonsignificant findings on parenting behavior–related intervening variables are astonishing, as parenting behavior is otherwise thought to be of paramount importance in the treatment of behavioral problems in youth, both in conventional interventions delivered face-to-face [75] and in digital parent training alike [76,77]. Therefore, the findings of our study are in contrast to those of a systematic review [75], which revealed that in 45% (39/86) of the included studies on face-to-face parent training programs, parenting behavior served as a mediator for the association between the intervention and symptom change in children. Furthermore, the importance of emotion regulation might be underestimated in (digital) psychotherapeutic interventions for children and adolescents, considering the consistent pattern of significant findings across studies in our review, as well as by allowing for comprehensive earlier research highlighting the overall importance of emotion regulation competencies for mental health in childhood and adolescence [78]. However, given the rather small number of mediation studies per category in our review, these findings need to be interpreted with caution and must be considered as preliminary. This is also owing to the rather heterogeneous evidence base, where included studies varied broadly in terms of the theoretical foundations of the intervention as well as the simultaneous consideration of various mental disorders, which may further restrict the comparability between studies. Nevertheless, a Wilcoxon rank-sum test revealed no differences in the sample sizes between studies that found at least one significant mediator and studies that found no significant mediator, suggesting that there is no effect of sample size on the evaluation of intervening variables, strengthening the robustness and validity of the findings on the mediators in this regard.

Importantly, participants were most often adolescents, with only 16% (4/25) of eligible studies evaluating interventions for children, suggesting an additional research gap for this younger age group. Here, all interventions for children were conducted with the involvement of parents, suggesting a crucial role of the accompanying human support in DHIs for younger children, which must be corroborated and further specified by forthcoming research [12,79]. In studies evaluating DHI_{HP}, only cognitive mediators (perceived norm and alcohol-related expectation) were investigated. This finding is consistent with prior research, where the cognitive mediator, perceived norm, was established as one of the most evaluated mediators in interventions for problematic drinking behaviors in adolescents and young adults delivered on site [80]. However, this result rather highlights the researcher's presumptions than the evidence base of the superior relevance of cognitive mediators over other, not yet well examined, affective and behavioral mediators.

The results of the RoB assessment indicated a rather limited overall study quality, with 76% (19/25) of the included studies rated with a *high RoB*, a finding that aligns with the review by Christ et al [81], in which 92% (22/24) included studies on DHIs for adolescents and young adults were assessed with a *high RoB*. These findings on RoB2 might be largely due to the specifics of psychotherapy research [82], where masking of therapists or personnel and participants is difficult to achieve, as well as the more conservative novel RoB2 algorithm [83]. Of note, in our review, the mean study dropout rate was 18%. Therefore, only a fraction of the included studies fulfilled the RoB2 criterion that 95% of randomized participants' data should be available for data analysis. Although the current mean dropout rate in this review is rather small compared with other high dropout rates found in DHIs, the well-known issue of limited engagement still warrants future research to further investigate approaches to remedy (study and intervention) attrition [84,85]. In this particular field, primary studies in the review at hand may offer guidance and direction to more effective engagement in youth (Multimedia Appendix 2), such as interactive intervention components and age-appropriate content presentation in the form of puzzles, videos, or cartoons [12].

The results of the methodological quality assessment for process research revealed that most studies adhered to certain quality criteria satisfactorily (ie, using an RCT design and CG, evaluation of a strong statistical association, describing a theoretical foundation for mediators and sample size per trial group). However, in contrast, most primary studies did not experimentally manipulate the potential mediators, did not assess several mediators simultaneously, and did not evaluate the time sequence or temporal ordering of changes in mediators and outcomes. However, this latter criterion is considered to be of utmost importance for causal inferences and is sometimes referred to as the *fifth step* of mediation analysis [86]. Even though mediators and outcomes were assessed more than twice in 60% (15/25) of the included studies, only 4% (1/25) of the studies [47] actually conducted a statistical evaluation of the time sequence of cause and effect. Taken together, the findings of our review seem to be in line with those of other research [24,44,45,83], pointing to important methodological

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shortcomings of mediation studies, which should be amended by future research. At this point, 1 high-quality RCT [58] sets an example, fulfilling 6 out of 8 quality criteria.

Strengths and Limitations

This systematic review offers several strengths, including a comprehensive literature search, as well as the broad consideration of common mental disorders and theoretical orientations, resulting in an extensive overview of the research on mediators and mechanisms of change for DHIs in children and adolescents conducted so far. Furthermore, with the differential consideration of the 2 categories of DHI_{PSY} and DHI_{HP}, we intended to provide specific evidence-based information that might be valuable for digital psychotherapeutic and health promotion interventions alike. However, some limitations must be considered when interpreting the findings of this review. First, the number of eligible studies is rather small; the generalizability of the findings might be reduced as most studies were conducted in Western countries; these studies evaluated internet-based interventions; participants were predominantly female; and these studies relied on older participants. Second, only English language papers were included, and we did not incorporate gray literature in our study as recent findings indicated a negligible relevance of gray literature in systematic reviews [87]; further, publication bias cannot be ruled out. Third, although we only included RCT studies in our review (which might have led to an overestimation of the study quality in general, omitting other design studies with potentially lower methodological rigor), the RoB assessment indicated substantial shortcomings in the included studies. However, this finding should be weighed against the typical constraints of research on psychological interventions.

Future Directions

The following recommendations might be helpful for future mediation studies, aiming to advance our understanding of the working mechanisms of DHIs for youth. First, it is essential to avoid the methodological shortcomings outlined in the assessment of quality criteria for process research, especially with regard to the temporality of changes and experimental manipulation of mediators, both of which are key for the justification of causal inferences. Furthermore, future studies should resort to more sophisticated and current methods of mediation analysis (eg, Grimm et al [88] and Hofmann et al [89]), ideally capable of clarifying temporal precedence and illustrating the actual pattern of change [24]. Second, the therapeutic or working alliance (ie, the professional relationship between therapists and patients; eg, Grawe et al [90]) was not evaluated as a mediator in any of the included studies. However, the recent development of the working alliance inventory for digital interventions [91] may contribute to future process research, informing the evidence base of the effects of a *digital* therapeutic alliance in DHIs for youth [37,92]. Furthermore, mediators that have not been investigated so far, such as behavioral and biological variables, should be evaluated in future studies. At this point, the possibilities of novel technological methods in process research seem not to be fully exploited in this research field [37]. Passive sensing methodologies and digital phenotyping approaches with smartphones [93] might generate insights on behavioral and biological mechanisms in real life, in addition to the predominant information on cognitive variables derived from self-reports identified in the current review. Third, although worldwide about 90% of youth live in countries with low or medium income, 90% of RCTs investigating mental disorders in children and adolescents are conducted in high-income countries [1], mirroring the findings of the review at hand. In contrast, the presumed advantages of DHIs may be especially relevant in structurally weak and low-income countries. To overcome this contradiction, replication studies should aim to include and reach populations from low-income countries as well. Finally, our review revealed that mediators focusing on emotional and cognitive processes might be of paramount importance as potential mechanisms of change in DHIs for youth. However, the processes covered by these mediators varied to some extent. Thus, future studies focusing on both emotional and cognitive processes in a systematic way within one framework could be of great importance for the field.

Conclusions

This systematic review is the first to comprehensively investigate the mechanisms of change in different DHIs for youth. The key findings indicate that the largest group of examined mediators are cognitive variables, followed by an array of other mediator variables, including interpersonal, parenting behavior, and affective mediator categories. Of note, emotional and affective mediators consistently reached statistical significance across studies, whereas parenting-related mediators were evaluated constantly as nonsignificant. However, these findings must be considered cautiously, as we detected only a limited number of primary studies, despite including a broad range of mental disorders and interventions. Future studies should aim to lessen this research gap, ideally adhering to the quality criteria for process research and recent methods of mediation analyses, enabling more causally robust findings. These forthcoming studies might contribute to disentangling the therapeutic processes in DHIs, providing evidence-based knowledge to inform intervention development and augmented mental health care practices worldwide.

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Authors' Contributions

MD, SE, and HB developed the study design. SE and HN conducted the systematic literature searches, extracted the data, and rated the risk of bias and methodological quality criteria of included studies under the supervision of MD. MD wrote the first draft of the manuscript. All authors (MD, SE, HN, AL, AB, and HB) have contributed to the writing of the manuscript and have approved the final manuscript.

Conflicts of Interest

AB has received payment for consulting from Pro-Change Behavior Systems. All other authors (MD, SE, HN, AL, and HB) stated no conflicts of interest.

Multimedia Appendix 1

Search strings for Cochrane Central Register of Controlled Trials, Embase, MEDLINE, and PsycINFO in Ovid.
[DOCX File , 64 KB-Multimedia Appendix 1]

Multimedia Appendix 2

Study characteristics.
[DOCX File , 113 KB-Multimedia Appendix 2]

Multimedia Appendix 3

Studies with number of criteria met.
[DOCX File , 68 KB-Multimedia Appendix 3]

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Abbreviations

CG: control group
DHI: digital health intervention
DHIHP: digital health intervention with a focus on health promotion
DHIPSY: digital health intervention with a psychotherapeutic focus
RCT: randomized controlled trial
RoB: risk of bias

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Chapter 10

Therapeutic processes in digital interventions for anxiety: A systematic review and meta-analytic structural equation modeling of randomized controlled trials

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Review



Therapeutic processes in digital interventions for anxiety: A systematic review and meta-analytic structural equation modeling of randomized controlled trials

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ABSTRACT

While the efficacy of Internet- and mobile-based interventions (IMIs) for treating anxiety disorders is well established, there is no comprehensive overview about the underlying therapeutic processes so far. Thus, this systematic review and meta-analysis evaluated research on mediators and mechanisms of change in IMIs for adult anxiety disorders (PROSPERO: CRD42020185545). A systematic literature search was performed in five databases (i.e., CENTRAL, Embase, MEDLINE, PsycINFO and ClinicalTrials.gov). Two reviewers independently screened studies for inclusion, assessed the risk of bias and adherence to quality criteria for process research. Overall, 26 studies ($N = 6042$) investigating 64 mediators were included. Samples consisted predominantly of participants with clinically relevant symptoms of generalized anxiety disorder and severe health anxiety, as well as of participants with non-clinically relevant anxiety symptoms. The largest group of examined mediators (45%) were cognitive variables, evincing also the second highest proportion of significance (19/29); followed in numbers by skills (examined: 22%; significant: 10/14) and a wide range of other (19%; 7/12), emotional/affective (11%; 2/7) and behavioral mediators (3%; 1/2). Meta-analytical synthesis of mediators, limited by a small number of eligible studies, was conducted by deploying a two-stage structural equation modeling approach, resulting in a significant indirect effect for negative thinking ($k = 3$ studies) and non-significant indirect effects for combined cognitive variables, both in clinical ($k = 5$) and non-clinical samples ($k = 3$). The findings of this review might further the understanding on presumed change mechanisms in IMIs for anxiety, informing intervention development and the concurrent optimization of outcomes. Furthermore, by reviewing eligible mediation studies, we discuss methodological implications and recommendations for future process research, striving for causally robust findings. Future studies should investigate a broader range of variables as potential mediators, as well as to develop and apply original (digital) process and engagement measures to gather qualitative and high-resolution data on therapeutic processes.

1. Introduction

Anxiety disorders – such as panic disorder, agoraphobia or generalized anxiety disorder – are among the most common mental disorders (Penninx, Pine, Holmes, & Reif, 2021; Remes, Brayne, van der Linde, & Lafortune, 2016) and constitute one of the leading causes of disability worldwide (James et al., 2018; Whiteford, Ferrari, Degenhardt, Feigin, & Vos, 2015). Anxiety disorders are associated with enormous personal suffering and impaired quality of life (Mendlowicz & Stein, 2000), high health care and economic costs (Andlin-Sobocki & Wittchen, 2005), high comorbidity with other mental disorders (Bandelow & Michaelis, 2015), as well as an elevated risk for suicidal ideation and behaviors (Sareen et al., 2005).

Psychological treatment options comprise different therapeutic

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approaches like psychodynamic therapy (Abbass et al., 2014; Slavin-Mulford, Hilsenroth, Weinberger, & Gold, 2011) or acceptance and commitment therapy (ACT; Landy, Schneider, & Arch, 2015), with cognitive behavioral therapy (CBT) evincing the best empirical support so far, as its efficacy and effectiveness for different anxiety disorders is supported in several meta-analyses to date (e.g., Bandelow et al., 2015; Hans & Hiller, 2013; Hofmann & Smits, 2008; Mayo-Wilson et al., 2014; Olatunji, Cisler, & Deacon, 2010; Stewart & Chambless, 2009). Despite these well-established treatment options, anxiety disorders remain underrecognized and undertreated (Bandelow & Michaelis, 2015), due to several barriers to psychotherapy utilization, including fear of social stigma, high treatment costs, or long waiting times for face-to-face psychotherapy and other mental health care services on-site (Andrade et al., 2014; Goetter et al., 2020; Mohr et al., 2010).

Digital psychotherapeutic interventions, such as Internet- and mobile-based interventions (IMIs), might offer solutions to some of the aforementioned treatment barriers and hold possible advantages over conventional psychotherapy: They allow easy and low-threshold access, can be used independently of time or location and might be cost-effective (Domhardt et al., 2020; Donker et al., 2015; Ebert et al., 2018). Furthermore, some IMIs grant users anonymity and might therefore reduce the perceived stigma threat when utilizing mental health care offerings and are potentially scalable to large numbers of patients (Gega, Marks, & Mataix-Cols, 2004; Berger, Boettcher, & Caspar, 2014). At this, IMIs can be differentiated by their technical implementation (e.g., smartphone-, tablet- or computer-based), way of application (e.g., stand-alone or blended care), degree of human support (e.g., pure self-help intervention or psychotherapy via video calls) and theoretical foundation (e.g., CBT or psychodynamic approaches; Domhardt, Ebert, & Baumeister, 2018; Ebert et al., 2018). Common to all IMIs is their aim to alter cognitive, behavioral and affective/emotional processes in the individual person, and the intention to support the transfer of these adaptations and acquired skills into the daily lifes of users (Domhardt et al., 2018; Ebert, Cuijpers, Muñoz, & Baumeister, 2017). The efficacy of both Internet-based and mobile-based interventions has been substantiated for treating anxiety disorder symptoms in different populations, with effect sizes for guided Internet-based interventions ranging from standardized mean differences (SMD) of −1.31 to −0.75 when compared to waitlist (Andrews et al., 2018; Domhardt, Letsch, et al., 2020; Domhardt, Steubl, & Baumeister, 2020; Olthuis, Watt, Bailey, Hayden, & Stewart, 2016) and unguided mobile-based interventions from SMD of −0.58 to 0.05 when compared to various control conditions (Linardon, Cuijpers, Carlbring, Messer, & Fuller-Tyszkiewicz, 2019). Internet-based CBT interventions with accompanying human support (i.e., guidance) evince even non-inferior results and comparable efficacy when compared to face-to-face psychotherapy (Carlbring, Andersson, Cuijpers, Riper, & Hedman-Lagerlöf, 2018; Domhardt, Letsch, et al., 2020; Olthuis et al., 2016).

In contrast to the well established efficacy of IMIs for anxiety disorders, knowledge on *whereby* or *how* these interventions elicit therapeutic change in patients has not been comprehensively investigated. Yet, evidence-based information on these issues is of high scientific and clinical relevance, as it can inform the optimization of interventions and mental health care practices, pointing to ways to more effective treatment programs with improved outcomes. In order to gain a better understanding of the mechanisms of change in psychotherapeutic interventions – irrespective if conveyed face-to-face or by technological means – component studies (Domhardt, Geßlein, von Rezori, & Baumeister, 2019) and mediation studies can be utilized (Domhardt et al., 2021).

In component studies (Borkovec & Costonguay, 1998), the distinct effect of single intervention components can be determined by directly comparing a complete psychotherapeutic intervention with the same intervention, in which either a component is left out (i.e., dismantling studies) or added to the full treatment package (i.e., additive design studies). Intervention components with relevant effect sizes (i.e., "active ingredients") can be further categorized, if they relate either to specific or to common factors of psychotherapies. Specific factors refer to components, which are characteristic and innate only to certain psychotherapeutic treatment approaches (e.g., cognitive restructuring for CBT); whereas common factors are present across different psychotherapeutic orientations and treatment modes (e.g., therapeutic alliance or expectations; Mulder, Murray, & Rucklidge, 2017). A recent meta-analysis on component studies in IMIs for anxiety found first preliminary indications that rather specific than common factors might play a crucial role for intervention efficacy. Yet, due to the limited number of eligible primary studies and concurrent low statistical power, specific effects of single intervention components were not detectable aside from guidance (Domhardt et al., 2019). Therewith, the results further corroborated the superiority of IMIs with accompanying human support compared to pure self-help interventions, which has been demonstrated across other mental disorders before (Baumeister, Reichler, Munzinger, & Lin, 2014).

However, knowledge derived from component studies does not entirely reveal *how* a treatment works, and which processes within patients lead to positive outcomes (Domhardt et al., in preparation). Mediation studies can reveal these crucial insights on change mechanisms and are often considered as the pivotal approach of psychotherapy process research (Domhardt, Steubl, et al., 2021). By means of mediation analyses it can be examined, if a mediator variable statistically accounts for the relationship between treatment and outcome. Thereby, a mediator might point to (or is identical with) a possible mechanism of change (i.e., the steps, processes or events within patients leading to change in the outcome), but may be also a proxy or agent for one or more other variables actually representative for the true mechanism (Kazdin, 2007).

Although there are numerous options to test for intervening variable effects (i.e., mediation; e.g., Hayes & Rockwood, 2017; MacKinnon, Kisbu-Sakarya, & Gottschall, 2013; Preacher, 2015), the causal steps approach by Baron and Kenny (1986) is still the most commonly employed procedure to statistically evaluate mediators to date – despite having received criticism, for example concerning limited statistical power, difficulties in the assessment of multiple mediators, omitting possible confounders, or quantification of mediation effects' magnitude (Fritz & MacKinnon, 2007; Mayer, Thoemmes, Rose, Steyer, & West, 2014; Preacher & Hayes, 2008b; Preacher & Kelley, 2011). According to the causal steps approach, mediation in the context of psychotherapy research is established when four conditions are fulfilled: (1) treatment and outcome are significantly related (i.e., total effect or c-path), (2) treatment is significantly related to the mediator (i.e., a-path), (3) the mediator is significantly related to the outcome (i.e., b-path) and (4) after controlling for the mediator, the previously significant relationship between treatment and outcome is absent (full mediation) or lessened (partial mediation; i.e., c'-path). Thereupon, the mediation effect (i.e., indirect effect) can be computed with the product of the a- and b-paths (Woody, 2011).

Nevertheless, statistical mediation alone is not sufficient to determine a mechanism and substantiate causality. Fundamentally, Kazdin (2007) introduced seven requirements for psychotherapy process research that have to be acknowledged when establishing evidence for a change mechanism and for inferring causality: (1) *Strong association* (between treatment, mediator and outcome), (2) *specificity* (a single mediator accounts for the indirect effect of treatment on outcome), (3) *consistency* (the association must be replicable across studies and samples), (4) *experimental manipulation* (utilization of either a randomized controlled trial (RCT) design where the intervention variable is manipulated, or an experimental design where the mediator is directly manipulated itself), (5) *timeline* (the intervention must lead to changes in the mediator, which must temporally precede changes in the outcome), (6) *gradient* (i.e., a dose-response relationship: greater activation of a mediator is associated with greater change in the outcome), and (7) *plausibility or coherence* (the proposed mediator must be embedded in a

plausible theoretical framework). Additionally, we suggest that the observance of possible confounding variables in statistical mediation analyses further strengthens the robustness of causal inferences and conclusions (Mayer et al., 2014); and that some of the initial criteria proposed by Kazdin (2007; i.e., specificity, consistency and gradient) might be too narrow for some mechanisms, considering the particular dynamics and complexities of psychotherapy processes (Domhardt & Baumeister, 2021; Domhardt, Steubl, et al., 2021; Hofmann, Curtiss, & Hayes, 2020). What is more, some scholars (e.g., Huibers, Lorenzo-Luaces, Cuijpers, & Kazantzis, 2021) argue that additional research is necessary to appraise and examine Kazdin's criteria more comprehensively; as well as for conceptual work that explores new quality criteria, which have the potential to statistically and methodologically advance the field of (digital) psychotherapy process research.

The evidence base on change mechanisms in face-to-face psychotherapies for anxiety disorders is limited and no meta-analysis has been published to date. A single systematic review has investigated the role of threat reappraisal as a mediator of symptom change in CBT (Smits, Julian, Rosenfield, & Powers, 2012). Other research, focusing exclusively on CBT, found significant mediators like fear of fear (Smits, Powers, Cho, & Telch, 2004), expectancy change (Newman & Fisher, 2010) or experiental avoidance in primary studies (Eustis et al., 2019). Furthermore, intervening variables like cognitive reappraisal (Kocovski, Fleming, Hawley, Ho, & Antony, 2015) or social cost (Hofmann, 2004) have been found to mediate treatment outcomes in cognitive behavioral group therapy. Additionally, cognitive defusion (Arch, Wolitzky-Taylor, Eifert, & Craske, 2012) and negative cognitions (Niles et al., 2014) have been reported as mediating variables both in ACT and CBT. Experiential avoidance has also been examined and reported as a mediator in acceptance-based behavior therapy and applied relaxation (Eustis, Hayes-Skelton, Roemer, & Orsillo, 2016). In a mindfulness-based stress reduction intervention the mediators decentering and mindfulness were identified (Hoge et al., 2015).

However, there is neither a systematic review nor a meta-analysis evaluating mediators in IMIs for anxiety disorders to date. While mediators of treatment change in other mental disorders like depression have already been systematically reviewed both in face-to-face-psychotherapy (Lemmens, Müller, Arntz, & Huibers, 2016) and in IMIs (Domhardt, Steubl, et al., 2021), comprehensive evidence for the anxiety disorders is pending. Therefore, the current meta-analytic review is intended to contribute to the understanding of how IMIs for anxiety work, informing the development of optimized intervention packages and improvement of treatment outcomes, as well as to also possibly contribute to raise treatment utilization (Berger, 2016; Cuijpers, 2016; Kazdin, 2007; Mogoase, Cobeanu, David, Giosan, & Szentagotai, 2017; Moldovan & Pintea, 2015). Furthermore, the investigation of change mechanisms in IMIs for anxiety might also ancillary lead to the identification of treatment moderators (Kazdin, 2007; Moldovan & Pintea, 2015), informing precision digital mental health (Domhardt, Cuijpers, Ebert, & Baumeister, 2021).

All in all, this is the first systematic review and meta-analysis on therapeutic processes in IMIs for adult anxiety disorders, aiming

1. to systematically review and methodologically assess studies that investigated mediators and mechanisms of change in IMIs for anxiety disorders,
2. to meta-analytically examine the specific effect sizes of mediators, and
3. to evaluate, if intervening variable effects are moderated by

a) participant characteristics,
b) type of anxiety disorder, or
c) type of psychotherapeutic approach (i.e., theoretical orientation).

2. Methods

This systematic review and meta-analysis is reported according to the PRISMA guidelines (Moher, Liberati, Tetzlaff, & Altman, 2009). The study protocol for this review has been a priori published (https://osf.io/qbmtp/) and pre-registered with PROSPERO (CRD42020185545). Differences between the final conduction of the review and the study protocol are listed in Appendix A in the supplemental data online.

2.1. Eligibility criteria

Studies were eligible for inclusion, if they fulfilled the following criteria:

2.1.1. Population

(1) Study participants had to be adults (≥18 years, no upper limit; in case of mixed samples including both adolescents and adults, the mean age had to be ≥18 years), (2) with a diagnosed anxiety disorder (e.g., specific phobia [SP], social anxiety disorder [SAD], panic disorder [PD], agoraphobia [A], or generalized anxiety disorder [GAD]), according to criteria from established classification systems, e.g., the Diagnostic and Statistical Manual of Mental Disorders (DSM-5; American Psychiatric Association, 2013) or the International Classification of Diseases (ICD-10; World Health Organization, 1992). The diagnosis could have been ascertained by structural clinical interviews (e.g., structured clinical interview for DSM-5 [SCID]; First, Williams, Karg, & Spitzer, 2015), standardized observer-rated instruments with normed cut-off points, validated self-report measures, or ratings by professional mental health care professionals (e.g., clinical psychologists, psychotherapists or psychiatrists). Although sufferers of clinically relevant health anxiety commonly qualify for a diagnosis listed in the Somatic symptom and related disorders chapter of the DSM-5 (American Psychiatric Association, 2013) or as belonging to the somatoform disorders of the ICD-10 (World Health Organization, 1992), several researchers and cognitive-behavioral theorists are advocating the classification of health anxiety within the category of anxiety disorders (Axelsson, Hesser, Andersson, Ljótsson, & Hedman-Lagerlöf, 2020; Olatunji, Deacon, & Abramowitz, 2009; Scarella, Laferton, Ahern, Fallon, & Barsky, 2016). Thus, it seemed meaningful to include studies about health anxiety too, in order to review the research question at hand as comprehensively as possible. (3) Studies investigating non-clinical samples (i.e., assessment of anxiety symptoms without applying a clinical cut-off score) were also eligible for inclusion, but were reported separately. (4) Additionally, studies examining participants with comorbid mental or somatic disorders alongside the primary anxiety disorder were eligible as well. (5) Furthermore, studies investigating multiple mental disorders, and therefore including just a subset of relevant participants with an anxiety disorder, were included too, if specific subgroup information for participants with an anxiety disorder were reported, and/or if the particular anxiety disorder or anxiety disorders in general were specified as the main indication of interest.

2.1.2. Intervention

(6) The intervention had to be provided in an Internet- and/or mobile-based setting. Apart from a possible initial face-to-face meeting or phone call, the Internet needed to be the only communication medium. In line with Berger (2016), the following three variations of IMIs were eligible for inclusion: (a) unguided self-help, (b) guided self-help (i.e., the Internet intervention is enriched with human support) and (c) Internet-based psychotherapy (e.g., via e-mail, chat or videoconference). (7) Furthermore, the intervention ought to be based on established psychotherapeutic approaches (e.g., CBT, psychodynamic therapy or ACT).

2.1.3. Comparison

(8) Studies had to include either an (a) active control group (e.g., alternative IMI, face-to-face psychotherapy, treatment-as-usual [TAU] or placebo) or a (b) non-active control group (e.g., waitlist control group [WLC] or no intervention).

2.1.4. Outcomes

(9) Possible mediators had to be assessed with validated psychometric instruments (e.g., credibility and expectancy questionnaire; Borkovec & Nau, 1972; Devilly & Borkovec, 2000). (10) Included studies needed to report anxiety symptom severity at post-treatment, measured either on a standardized observer-rated instrument (e.g., Hamilton anxiety rating scale; Hamilton, 1959) or a validated self-report instrument (e.g., Beck anxiety inventory; Beck, Epstein, Brown, & Steer, 1988). These measures could encompass anxiety symptoms in general or symptoms for a specific anxiety disorder. (11) Additional outcomes included adherence to the intervention and dropouts. (12) In case of multiple instruments on the same hierarchical level (observer-rated or self-report) in one study, the instrument with better psychometric properties was selected.

2.1.5. Study design

(13) Only RCTs that included adequate mediation analyses (e.g., Baron and Kenny (1986) or more recent alternative approaches to mediation analyses) were eligible for inclusion. Additionally, secondary analyses on already published RCTs were eligible as well, if appropriate mediation analyses were conducted.

2.1.6. Publication type

(14) Studies had to be written in English and (15) published in a peer-reviewed journal or classified as ongoing trial with already available results on ClinicalTrials.gov or the WHO International Clinical Trials Registry Platform (ICTRP).

2.2. Search strategy

A systematic search of the electronic databases Cochrane Central Register of Controlled Trials (CENTRAL), Embase, MEDLINE, and PsycINFO was conducted initially on May 12th 2020 and updated on July 4th 2021 via the Ovid interface. Terms indicative of "anxiety", "Internet", "digital", "psychotherapy", "RCT", "mediators", "mechanisms" and "processes" were combined (see Table B.1 in the Appendix within the supplemental data for detailed information on all search strings). The search strategy was adapted from previous reviews and adjusted to suit the current research focus accordingly (Domhardt et al., 2019; Domhardt, Steubl, et al., 2021). Furthermore, ClinicalTrials.gov was searched to identify currently ongoing trials with already available results using specific search strings (see Table B.2). Additionally, backwards citation searching (i.e., identifying studies cited by the source study) and forwards citation searching (i.e., identifying studies which refer to an already included primary study) were performed using the Web of Science database for all eligible studies. Due to the Covid-19 pandemic, the WHO ICTRP was not available for our systematic search (Appendix A).

Because no systematic review on mediators and mechanisms of change for anxiety disorders in face-to-face psychotherapy (comprising different theoretical orientations) has been conducted to date, relevant studies investigating this topic were extracted alongside the primarily focused digital health interventions, in order to have the opportunity to contrast the therapeutic processes in IMIs with those in psychotherapies delivered on-site.

2.3. Study selection process

First, the titles and abstracts of studies identified with the electronic database search were screened by one reviewer (HN). Irrelevant titles were excluded. Second, full text screening regarding the aforementioned eligibility criteria was executed by two independent reviewers (HN and SE). Studies resulting from backward and forward citation searches (conducted by HN), utilizing studies already identified as eligible, were also checked for suitability by both reviewers through full-text screening. Disagreements were resolved by discussion. If no consensus could be attained, a third reviewer (MD) was consulted. The software "Covidence" (Veritas Health Innovation, 2020) was used to detect and remove duplicates. Remaining duplicates were removed manually. Details illustrating the study selection process and reasons for exclusion are presented in a PRISMA flow chart in Fig. 1.

2.4. Data extraction

The following data were extracted from included studies independently by two reviewers (HN and SE) using a piloted structured form: (1) study identification items (e.g., first author, year of publication), (2) sample characteristics (e.g., type, anxiety disorder), (3) characteristics of IMIs (e.g., underlying psychotherapeutic orientation, duration in weeks), (4) comparison groups (e.g., type, size), (5) outcome characteristics (e.g., instruments, time points of follow-ups), (6) study design features (e.g., sample size, recruitment strategy), and (7) mediator attributes (e.g., statistical mediation analysis, instruments). In case of missing data, we contacted the corresponding authors of eligible primary studies for relevant additional information.

2.5. Quality assessment

In a first step, the risk of bias assessment was conducted by two independent reviewers (HN and SE) according to the revised Cochrane risk of bias tool for randomized trials (RoB 2; Sterne et al., 2019). The following criteria were rated for each study: (1) "randomization process", (2) "deviations from intended interventions", (3) "missing outcome data", (4) "measurement of the outcome", (5) "selection of the reported results" and (6) "overall bias". Each study was rated to either display "low risk of bias", "some concerns" or "high risk of bias" concerning the aforementioned criteria (Sterne et al., 2019). Disagreements between the two assessors were discussed. If no consensus could be reached, a third reviewer (MD) was consulted.

Second, a rating system for demonstrating an adequate study design to detect mechanisms of change and approximate causality – originally introduced by Kazdin (2007) and adjusted by Lemmens et al. (2016) and Domhardt, Steubl, et al. (2021) – was applied. Studies had to (1) use an appropriate RCT design, (2) include a control group, (3) report a theoretical foundation for mediators, (4) have a minimum sample size of 40 participants per group, (5) examine multiple mediators within one study, (6) assess temporality (three or more assessments of the mediator variables and outcomes) and (7) experimentally manipulate the mediator in order to meet criteria for process research. Additionally, (8) strong statistical association between treatment, mediator and outcome (operationalized as statistical significance of $p < .05$, as suggested by Moreno-Peral et al., 2020) was evaluated. Finally, (9) we added another criterion to Kazdin's initial criteria, in order to assess whether the primary studies considered and controlled for confounding variables in a methodologically appropriate manner (Mayer et al., 2014). All criteria were rated as fulfilled or not fulfilled. In accordance with Lemmens et al. (2016) and Domhardt, Steubl, et al. (2021), the aspects specificity, consistency and gradient were not assessed, since they are not meaningfully applicable in single studies (consistency) or too exclusive for certain therapeutic processes (gradient and specificity). Yet, these aspects are addressed in the discussion section.

2.6. Data synthesis

Since conventional meta-analyses do not allow for the evaluation of mediation effects (Tang & Cheung, 2016), a two-stage structural equation modeling (TSSEM) approach (Cheung, 2020; Cheung & Chan, 2005) was chosen in the current study in order to investigate the second review aim. The TSSEM approach was chosen because it holds advantages in contrast to other strategies (e.g., generalized least squares or univariate methods). When conducting TSSEM, correlation matrices between intervention, mediator and outcome are synthesized across

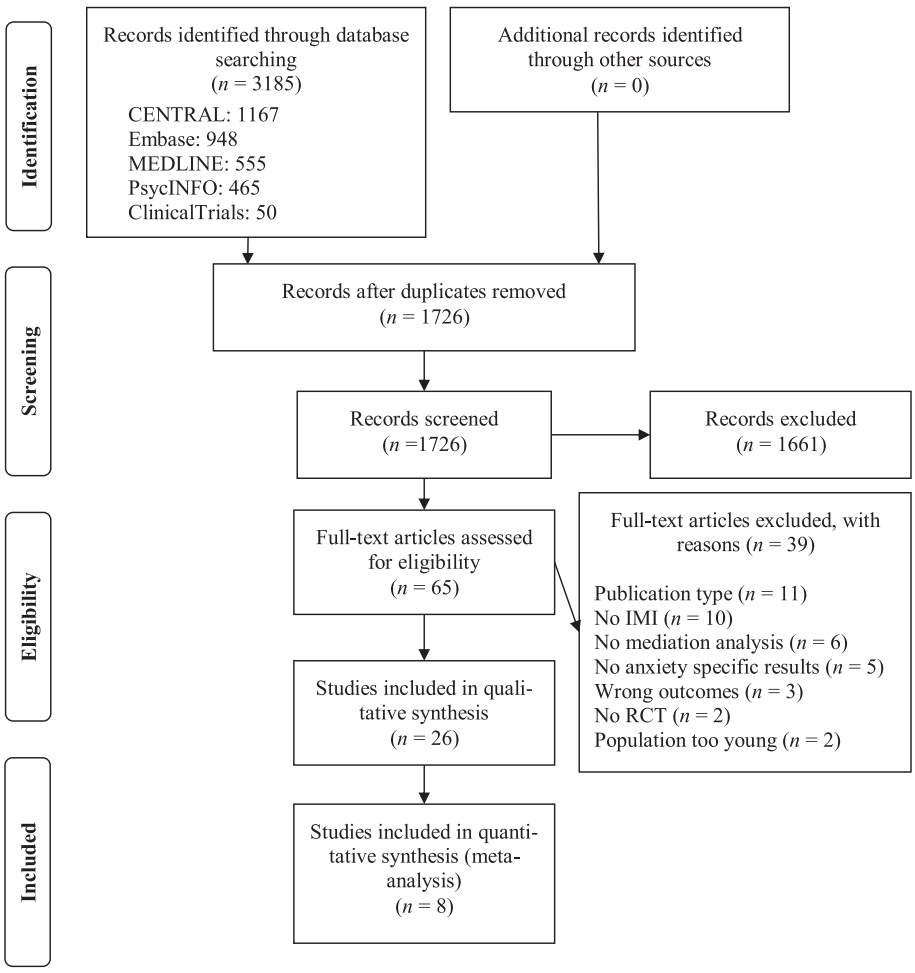


Fig. 1. Flow of study selection in the current review. CENTRAL = Cochrane Central Register of Controlled Trials; IMI = Internet- and mobile-based intervention; RCT = Randomized controlled trial; Adapted from "Preferred Report-ing Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement", by D. Moher, A. Liberati, J. Tetz-laff, D. G. Altman and The PRISMA Group, 2009, PLoS Med, 6(7): e1000097.

studies in a first step, and mediation models are fitted on the pooled correlation matrix with a weighted least squares approach (Cheung & Chan, 2005).

In line with Gu, Strauss, Bond, and Cavanagh (2015), meta-analyses were conducted, if three or more studies had evaluated mediators with nearly identical or sufficiently similar concepts. For this purpose, mediators were categorized into groups with either (a) high or (b) sufficient conceptual overlap. If included studies did not report bivariate correlations between treatment, mediator and outcome, reported statistics were used to calculate them (Borenstein, Hedges, Higgins, & Rothstein, 2009) with the R package *esc* (version 0.5.1; Lüdecke, 2019). If a study contained insufficient data to calculate correlations and relevant data could not have been provided by study authors, it was excluded from the analyses. The *metaSEM* package (version 1.2.4; Cheung, 2015b) and recent approaches to TSSEM (Cheung, 2020) were used to conduct the TSSEM analyses. In all analyses, random-effects models were used to accommodate the clinical, methodological and statistical heterogeneity between the included studies (Cheung, 2014). In this context, we followed the default settings in *metaSEM*, which assumes separate but uncorrelated random effects for each correlation coefficient. To address convergence issues (e.g., variances estimated as zero), we further constrained the model as needed to achieve convergence (e.g., by fixing variance components to zero). To assess the significance for the indirect, direct and total effects, 95% likelihood-based confidence intervals (CIs), holding various advantages against Wald approximation-based CIs (Cheung, 2015a), were used in the current study.

Statistical heterogeneity was assessed with the Cochran's *Q*-test and quantified through the I^2 statistic (Borenstein, Higgins, Hedges, & Rothstein, 2017; Higgins, Thompson, Deeks, & Altman, 2003). According to the Cochrane handbook for systematic reviews of interventions, an I^2 from 0% to 40% might not be important, 30% to 60% may indicate moderate heterogeneity, 50% to 90% may indicate substantial heterogeneity and 75% to 100% suggests considerable heterogeneity (Deeks, Higgins, & Altman, 2020).

Data analyses were performed with the statistical program R (version 4.0.3; R Core Team, 2020). Inter-rater reliabilities (using Cohen's Kappa) were computed for data extraction, risk of bias assessment and the criteria for process research using the R package *irr* (version 0.84.1; Gamer, Lemon, Fellows, & Singh, 2019).

3. Results

3.1. Study selection

The systematic database search yielded 3185 results in total. After removal of duplicates and screening of titles and abstracts, 65 studies were assessed for eligibility in full-text review. Of those, 26 trials (with 6042 participants) met the criteria for inclusion. Forward and backward searches did not produce additional papers. All references of included studies can be found in the supplementary data (Appendix C). Potentially relevant study registrations and/or protocols, which were not completed so far, are depicted in Table B.3 in the supplement. Although

these ongoing studies could not be included in the current review, they might be of relevance in future reviews and contribute to knowledge about change mechanisms in IMIs for anxiety prospectively.

3.2. Study characteristics

A detailed overview of study characteristics can be found in Table B.4 in the supplement. In total, 6042 participants were investigated in primary studies with sample sizes ranging from $n = 44$ to $n = 1162$ (median = 156; $SD = 240$). The sample size adjusted mean age of participants was $M = 35.99$ ($SD = 3.22$), calculated from studies providing these data. Participants were predominantly female (75.58%). Most of the included studies were published within the past five years (2015–2020; $k = 19$; 73.08%), and almost all studies were conducted in western countries (92.30%): Australia ($k = 8$; 30.77%), USA ($k = 5$; 19.23%), Germany ($k = 3$; 11.54%), Sweden ($k = 3$; 11.54%), the Netherlands ($k = 3$; 11.54%) and the UK ($k = 2$; 7.69%). Two studies were conducted in China ($k = 2$; 7.69%).

Samples with clinically relevant anxiety symptoms ($n = 1784$; 29.53%) were investigated in nine studies and non-clinical samples in 13 studies ($n = 3801$; 62.91%). Samples with severe health anxiety ($n = 457$; 7.56%) were examined in four studies. Among clinical samples, GAD was most frequently examined ($k = 5$; 55.56%), followed by samples investigating self-reported clinically relevant anxiety symptoms ($k = 2$; 22.22%) and SAD ($k = 2$; 22.22%). In non-clinical samples, anxiety symptoms were examined with the GAD-7 in four studies (30.77%) and with the CCAPS-34 in one study (7.69%). The remaining studies investigating non-clinical samples assessed anxiety symptoms with other general anxiety severity instruments ($k = 8$; 61.54%), like the HADS-A ($k = 2$; 15.38%) or SAS ($k = 1$; 7.69%).

Internet-based interventions were evaluated in 23 studies (88.46%). Only two studies implemented an intervention combining Internet- and mobile-based components ($k = 2$; 7.69%), and a single study investigated an exclusively mobile-based intervention (3.85%). Most interventions were based on CBT principles ($k = 11$; 42.31%), followed by theoretical foundations of ACT ($k = 4$; 15.38%) or mindfulness-based cognitive therapy ($k = 2$; 7.69%). Further, four studies (15.38%) combined different psychotherapeutic approaches, including interpersonal psychotherapy, applied relaxation and problem-solving therapy. In two studies (7.69%), the temporal model of control constituted the theoretical underpinning of the intervention and the remaining studies used positive emotion regulation ($k = 1$; 3.85%), positive psychology ($k = 1$; 3.85%) and cognitive bias modification approaches ($k = 1$; 3.85%) as therapeutic foundations.

On average, interventions consisted of eight modules or sessions (ranging from four to 14 modules or sessions) with a mean duration of seven weeks (ranging from 1.4 to twelve weeks). Guided self-help was the most frequently utilized intervention format ($k = 17$; 65.38%), followed by unguided self-help without any human support ($k = 4$; 15.38%) and Internet-based therapy ($k = 3$; 11.54%). Two studies employed their interventions both in a guided and unguided format (7.69%). The outcome assessment of anxiety symptom severity was frequently conducted with the seven-item generalized anxiety disorder scale (GAD-7; Spitzer, Kroenke, Williams, & Löwe, 2006; $k = 8$; 30.77%), depression, anxiety and stress scales (DASS; Lovibond & Lovibond, 1995; $k = 4$; 15.38%), short or full version of the health anxiety inventory ((S)HAI; Salkovskis, Rimes, Warwick, & Clark, 2002; $k = 4$; 15.38%) or the hospital anxiety and depression scale - anxiety subscale (HADS-A; Zigmond & Snaith, 1983; $k = 3$; 11.54%). Control conditions consisted mostly of a WLC ($k = 15$; 57.69%) or in two cases of a WLC and an additional comparison group (7.69%). Several studies implemented an active comparison group, such as TAU or behavioral stress management ($k = 9$; 34.62%).

Primary studies evaluated 64 mediators in sum, ranging from one to seven investigated mediators per trial. Mediation analyses were conducted with various techniques – studies often utilized different versions of PROCESS (Hayes, 2017), bootstrapping or generally employed their analyses in line with the recommendations by Preacher and Hayes (2004, 2008a) or Hayes and Rockwood (2017; $k = 13$; 50.00%). Further, SEMs were implemented in seven studies (26.92%) for mediation analyses. Four studies (15.38%) explicitly stated to follow the criteria outlined by Baron and Kenny (1986). One study reported using multiple regression analyses without providing further detailed information (3.85%) and one study did not specify the technique for mediation analysis at all (3.85%).

Comorbidity and/or medication rates were reported in eight studies each. Adverse events were reported in five studies, and deterioration rates were calculated for three trials. Drop-out rates were on average 22.26% ($SD = 17.04\%$) across studies, ranging from no study dropouts to 68.06% (please refer to Table B.4 in the supplement for further details on study characteristics). Inter-rater reliability for data extraction yielded perfect agreement ($\kappa = 1.00$) on all categories.

3.3. Mediators

Of the 64 identified putative mediators, 39 were evaluated to be significant in the included primary studies ($p < .05$; 60.94%; see Table B.5 in the supplement). Details on the conceptual categorizations of the mediators are provided in Table 1.

With 29 cognitive mediators investigated in clinical, non-clinical and health anxious samples, this category represented the largest group among all examined mediators (45.31%). Behavioral mediators were investigated in a clinical and in a health anxious sample each, constituting the smallest group of mediators (3.13%). Further, seven emotional and affective mediators were examined in clinical and non-clinical samples (10.94%). In total, 14 skills were studied as putative mediators in clinical, non-clinical and health anxious samples (21.88%). The remaining twelve mediators were not clearly classifiable into one of the aforementioned categories and were thus gathered within an "other mediators" category (18.75%).

Of the cognitive mediators, 19 were established as significant (19/29). One mediator was found to be significant in the behavioral mediators group (1/2), and two mediators were evaluated as significant in the emotional/affective mediators group (2/7). In the group of skills as mediators, ten were found to be significant (10/14). Finally, more than half of the mediators classified as "other" were established as significant in primary studies (7/12). Mediators evaluated in trials that attended to the temporality criterion are indexed with the letter "t", and mediators that were directly manipulated in an experiment with the letter "e" in Table 1.

3.4. Risk of bias assessment and quality criteria for process research

Results of the risk of bias assessment are detailed in Figs. B.1 and B.2 in the supplement. The best met criterion was "missing outcome data" (89.00% of studies were rated as having low risk of bias), whereas "measurement of the outcome" had the highest risk of bias (57.00%). The latter finding is largely due to specific characteristics of (face-to-face) psychotherapy research, where masking of participants is impossible to be achieved (Munder & Barth, 2018), and self-report ratings might be prone to bias accordingly. Yet, since masking of participants and personnel might be principally possible in (unguided) digital interventions with two active conditions (Domhardt, Letsch, et al., 2020), we opted to rate this domain anyhow. The overall risk of bias assessment evinced a high risk of bias rating in the majority of studies (73.00%) or some concerns in the remaining studies (27.00%). The risk of bias ratings yielded overall a good agreement ($\kappa = 0.72$) between the two reviewers.

Detailed results of the quality assessment for process research are presented in Table 2 and Table B.6. The majority of studies fulfilled six or seven (out of nine) criteria ($k = 18$; 69.23%), while eight studies met five or less criteria (30.77%). All 26 studies employed an appropriate

Table 1
Categorization of mediators.

	Cognitive mediators	Behavioral mediators	Emotional and affective mediators	Skills as mediators	Other mediators
Clinical samples	*Anticipatory processing*[t] (n.s.) *Cost bias*[t] (n.s.) *Interpretation bias*[e] (+)[#] *Mental health self-efficacy* (+) *Perceived inferiority*[t] (n.s.) *Positive metacognitive beliefs about RNT*[t] (+) *Post-event processing*[t] (n.s.) *Probability bias*[t] (n.s.) *Psychological flexibility*[t, c] (+) *RNT*[~,t, d] (n.s.) *Self-criticism*[t] (n.s.) Thought-related distress (+)	Risk-taking (n.s.)	Activation of the soothing system[t] (n.s.) Shame proneness (+)	Activity scheduling (+) CBT skills usage (+) Rewarding behaviors (+) Skills of cognitive restructuring (+) Social interaction (n.s.)	–
Non-clinical samples	Cognitive fusion (+) Coping self-efficacy (+) Mastery (n.s.) *Obstruction to valued living* (+) Optimism (+) *Present control* (+) Present control[e,a] (+) Psychological flexibility[t, c] (+) *RNT*[~,t, b] (+) *Rumination* (+)[##] Values (+)	–	Emotion regulation difficulties (n.s.) Emotional self-awareness (n.s.) Positive emotion (n.s.) Positive emotion (n.s.) Self-compassion (+)	Acceptance (+) Acting with awareness (n.s.) Describing (n.s.) Mindful acceptance (+) Non-judging (+) Present moment awareness (+) Use of strengths (n.s.)	Depression (+) Mental health literacy (n.s.) Positive relations (+) Resilience (n.s.) Resilience[t, b] (n.s.) Therapeutic alliance (n.s.)
Health anxious samples	Attention to bodily sensations[t] (+) Intolerance of uncertainty[t] (+) Negative consequences of disease[t] (n.s.) Perceived competence in managing health anxiety[t] (+) Perceived risk[t] (+) Somatosensory amplification[t] (n.s.)	Health anxiety behaviors[t] (+)	–	Mindful non-reactivity (+) Non-reactivity to inner experiences (+)	Compulsion (+) Cyberchondria (+) Distress (+) Excessiveness (+) Mistrust (n.s.) Reassurance (+)

Note. Only italicized mediators were eligible for TSSEM analyses. RNT = Repetitive negative thinking; (+) = significant; (n.s.) = non-significant; – = no mediators in this category; [~] = These variables yielded different findings in different studies; [#] = Significant only for the SST (Scrambled sentences test; Wenzlaff & Bates, 1998, 2000; see Table A.4 for details); [##] = Significant only for students with a history of interpersonal violence (see Table A.4 for details); [t] = The criterion temporality was evaluated in this study; [e] = The mediator was experimentally manipulated.
[a] Hintz, Frazier, & Meredith, 2015.
[b] Heckendorf, Lehr, Ebert, & Freund, 2019.
[c] Fledderus, Bohlmeijer, Fox, Schreurs, & Spinhoven, 2013.
[d] Newby, Williams, & Andrews, 2014.

RCT design and included a control group, in accordance with the eligibility criteria for this systematic review and meta-analysis. The next best fulfilled criteria was theoretical foundation of mediators (k = 24; 92.31%), followed by the criteria of at least 40 participants per trial group (k = 22; 84.62%), strong statistical association (k = 21; 80.77%) and observance of possible confounders (k = 18; 69.23%). More than half of the included studies investigated multiple mediators (k = 14; 53.85%). Temporality and experimental manipulation of the mediator (s) were the least fulfilled criteria, with only seven (26.92%) and two (7.69%) studies adhering to these principles, respectively. The quality of included studies was nearly the same for studies with clinical (66.66% of all criteria were met across studies) and non-clinical (67.52%) samples, while studies with health anxious samples adhered to the criteria somewhat more (75.00%). Inter-rater reliabilities showed excellent agreement (κ = 1.00) on all of the criteria for process research.

3.5. TSSEM results

Starting from the overarching conceptual categorization of intervening variables into cognitive, behavioral, emotional/affective, skills and other mediators (Table 1), we strived to group mediators with either (a) high/identical or (b) sufficient conceptual overlap for TSSEM analyses. Although, we identified over 64 different intervening variables in primary studies, the mediators indicated limited conceptual similarities and meaningful overlap for meta-analytical syntheses. Furthermore, a substantial amount of mediators could not be included in TSSEM analyses, because correlation coefficients were not available (either from published studies or from personal consultation with corresponding authors) and could not be computed from the remaining information provided in the studies (e.g., path coefficients, mean differences). Therefore, only one category with (a) high conceptual overlap (negative thinking), and (b) two categories with sufficient conceptual overlap (combined cognitive mediators in clinical and non-clinical samples) were eventually eligible for TSSEM analyses (Table 3).

The mediators capturing the concept of negative thinking were investigated in three studies (Table 3), which could all be included in the TSSEM analysis with four effect sizes: Repetitive negative thinking (Heckendorf et al., 2019; Newby et al., 2014) and rumination (Nguyen-Feng et al., 2015), with the sample of Nguyen-Feng et al. (2015) being divided into participants with and without a history of interpersonal violence. The analysis yielded significant pooled correlations between treatment status (IMI vs. control) and negative thinking ($\rho_{TM} = -0.19$, $p = .031$), between negative thinking and anxiety severity ($\rho_{MY} = 0.25$, $p < .001$) and between treatment status and anxiety severity ($\rho_{TY} = -0.16$, $p = .020$), as well as heterogeneity ranging from low to substantial ($Q(6) = 41.8$, $p < .001$; I^2 for $\rho_{TM} = 85\%$; I^2 for $\rho_{TY} = 74\%$). The random effects variance for the relation between the mediator (negative thinking) and anxiety (ρ_{MY}) was fixed to zero ($I^2 = 0$), because the observed correlations had little variance and this was required to ensure convergence of the TSSEM procedure. In stage 2 of the analysis, both the effect of the treatment status on negative thinking (a = −0.194; 95%-CI: [−0.371, −0.018]) and the effect of negative thinking on anxiety (b = 0.230; 95%-

Table 2
Quality assessment for psychotherapy process research.

Study	RCT	Control group	Theoretical foundation	$n \geq 40$ per group	Multiple mediators	Temporality	Manipulation of mediators	Strong association	Observance of confounders	Number of criteria met
Clinical samples										
Clarke et al. (2014)	+	+	+	+	−	−	−	+	+	6
Fledderus et al. (2013)	+	+	+	+	−	+	−	+	+	7
Hirsch et al. (2018)	+	+	+	+	−	-[b]	+	+	+	7
LaFreniere & Newman (2019)	+	+	+	−	−	-[b]	−	+	−	4
Lorian, Titov, & Grisham (2012)	+	+	+	−	−	−	−	−	+	4
Newby et al. (2014)	+	+	+	+	+	+	−	+[d]	+	8
Stevenson, Mattiske, and Nixon (2019)	+	+	−	+	+	+	−	−	+	6
Terides, Dear, Fogliati, Gandy, Karin, Jones, & Titov (2018)	+	+	+	+	+	-[b]	−	+[d]	+	7
Wang, Zhao, Mu, Rodriguez, Qian, & Berger (2020)	+	+	+	+	−	−	−	+	−	5
Non-clinical samples										
Bakker, Kazantzis, Rickwood, & Rickard (2018)	+	+	+	+	+	−	−	+[d]	+	7
Heckendorf et al. (2019)	+	+	+	+	+	+	−	+[d]	+	8
Hintz et al. (2015)	+	+	+	+	−	-[b]	+	+	+	7
Knaevelsrud, & Maercker (2006)	+	+[a]	+	+	−	−	−	−	−	4
Levin, Haeger, Pierce, and Twohig (2017)	+	+	−	−	+	−	−	+[d]	+	5
Lin, Klatt, McCracken, & Baumeister (2018)	+	+	+	+	−	+	−	+	−	6
Ma, She, Siu, Zeng, & Liu (2018)	+	+	+	+	−	−	−	−	+	5
Moskowitz, Cheung, Snowberg, Verstaen, Merrilees, Salsman, & Dowling (2019)	+	+	+	+	−	−	−	−	−	4
Nguyen-Feng et al. (2015)	+	+	+	+	+	−	−	+[d]	+	7
Querstret, Cropley, & Fife-Schaw (2018)	+	+	+	+	+	−	−	+[d]	+	7
Schotanus-Dijkstra, Pieterse, Drossaert, Walburg, & Bohlmeijer (2019)	+	+	+	+	+	-[b]	−	+[d]	+	7
van der Zanden, Galindo-Garre, Curie, Kramer, & Cuijpers (2014)	+	+	+	+	+	-[b]	−	+[d]	−	6
Viskovich and Pakenham (2020)	+	+	+	+	+	-[c]	−	+[d]	−	6
Health anxious samples										
Axelsson et al. (2020)	+	+	+	−	+	+	−	+[d]	+	7
Hedman et al. (2013)	+	+	+	+	+	+	−	+[d]	+	8
Hedman et al. (2017)	+	+	+	+	−	-[b]	−	+	−	5
Newby & McElroy (2020)	+	+	+	+	+	−	−	+[d]	+	7

Note. + = criterion met; − = criterion not met.

[a] Knaevelsrud & Maercker (2006) employed a control group in their study, but did not use it for statistical analyses.

[b] In these studies, outcomes were measured on (more than) three time points, but temporal precedence was not established in data analyses.

[c] The authors did conduct a temporal mediation analysis, but included only the intervention group into it. Both intervention and control group were included only in concurrent mediation analysis.

[d] These studies investigated more than one mediator, of which at least one had a strong association with the intervention and outcome. For more details on significance of individual mediators, see Table A.4.

CI: [0.101, 0.357]) were statistically significant. In addition, the indirect effect of treatment status via negative thinking (ab = 0.045; 95%-CI: [−0.104, −0.004]) was also significant, whereas the direct effect of treatment status was not (c' = −0.116; 95%-CI: [−0.260, 0.035]; Fig. 2).

For the analysis on combined cognitive mediators within clinical samples, twelve mediators could be included into TSSEM analysis from five studies with twelve effect sizes (Table 3): Mental health self-efficacy (Clarke et al., 2014), psychological flexibility (Fledderus et al., 2013), interpretation bias (once assessed with the SST and once with the RT) (Hirsch et al., 2018), repetitive negative thinking and positive metacognitive beliefs about RNT (Newby et al., 2014), as well as perceived inferiority, self-criticism, anticipatory processing, post-event processing, probability bias and cost bias (Stevenson et al., 2019). In stage 1 of the analysis, only the pooled correlation between treatment status and anxiety was significant ($\rho_{TY} = -0.14$; $p = .002$; $\rho_{TM} = 0.02$, $p = .78$; $\rho_{MY} = -0.00$, $p = .91$). Heterogeneity was substantial to considerable ($Q(26) = 117$, $p < .001$; I^2 for $\rho_{TY} = 75\%$; I^2 for $\rho_{TM} = 84\%$). The random effects variance for the relation between the mediator (combined cognitive

Table 3
Mediators eligible for TSSEM.

Negative thinking (clinical and non-clinical samples)		Combined cognitive mediators (clinical samples)		Combined cognitive mediators (non-clinical samples)	
Studies	Mediators	Studies	Mediators	Studies	Mediators
Heckendorf et al. (2019)	Repetitive negative thinking ~,t (+)	Clarke et al. (2014)	Mental health self-efficacy (+)	Heckendorf et al. (2019)	Repetitive negative thinking~,t (+)
Newby et al. (2014)	Repetitive negative thinking ~,t (n.s.)	Fledderus et al. (2013)	Psychological flexibility[t] (+)	Levin et al. (2017)	Obstruction to valued living (+)
Nguyen-Feng et al. (2015)	Rumination (+)##	Hirsch et al. (2018)	Interpretation bias[e], as assessed with the SST (+)	Nguyen-Feng et al. (2015)	Present control (+)
			Interpretation bias[e], as assessed with the RT (n.s.)		
		Newby et al. (2014)	Repetitive negative thinking ~,t (n.s.)	Nguyen-Feng et al. (2015)	Rumination (+)#
		Newby et al. (2014)	Positive metacognitive beliefs about RNT[t] (+)		
		Stevenson et al. (2019)	Perceived inferiority [t] (n.s.)		
		Stevenson et al. (2019)	Self-criticism[t] (n.s.)		
		Stevenson et al. (2019)	Anticipatory processing[t] (n.s.)		
		Stevenson et al. (2019)	Post-event processing[t] (n.s.)		
		Stevenson et al. (2019)	Probability bias[t] (n.s.)		
		Stevenson et al. (2019)	Cost bias[t] (n.s.)		

Note. RNT = Repetitive negative thinking; (+) = significant; (n.s.) = non-significant; ~ = These variables yielded different findings in different studies; # = Significant only for students with a history of interpersonal violence (see Table A.4 for details); [t] = The criterion temporality was evaluated in this study; [e] = The mediator was experimentally manipulated.

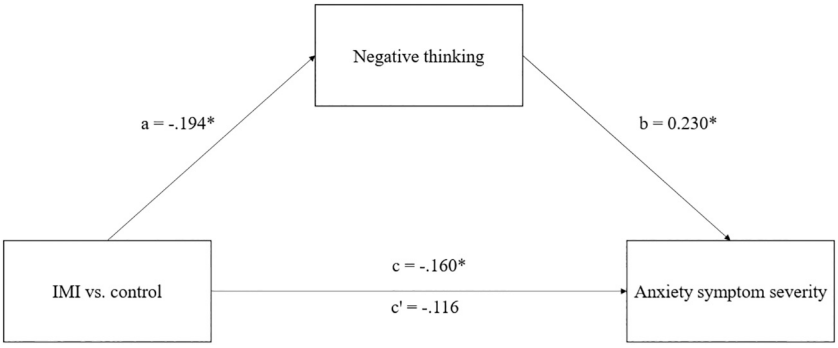


Fig. 2. Path diagram displaying the stage two mediational model of the TSSEM for negative thinking. Values are path coefficients. *Parameter estimates are significantly different from zero (i.e., 95%-CIs do not contain zero).

variables) and anxiety (ρ_{MY}) was fixed to zero ($I^2 = 0$) because this was required to ensure convergence of the TSSEM procedure. In stage 2 of the analysis, the a-, b- and the indirect effect were non-significant (a = 0.017; 95%-CI: [−0.104, 0.139]; b = −0.002; 95%-CI: [−0.076 0.073]; ab = −0.000; 95%-CI: [−0.005, 0.006]). Only the direct effect was evaluated as significant (c' = −0.143; 95%-CI: [−0.233, −0.052];

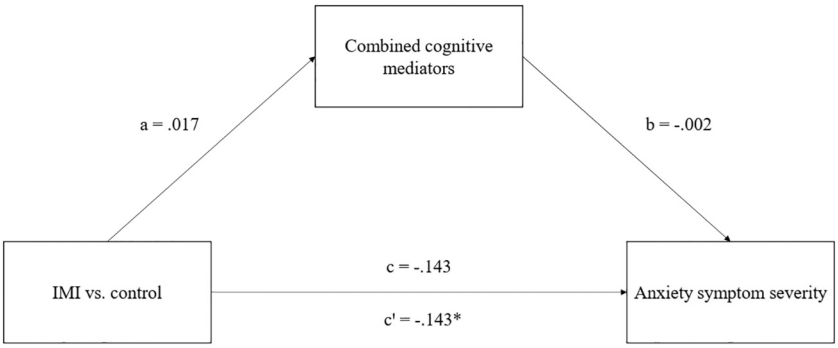


Fig. 3. Path diagram displaying the stage two mediational model of the TSSEM for combined cognitive mediators in clinical samples. Values are path coefficients. *Parameter estimates are significantly different from zero (i.e., 95%-CIs do not contain zero).

Fig. 3).

In non-clinical samples, four out of eleven cognitive mediators could be included into the TSSEM analysis on combined cognitive mediators from three studies with four effect sizes (Table 3): Repetitive negative thinking (Heckendorf et al., 2019), obstruction to valued living (Levin et al., 2017), present control and rumination (Nguyen-Feng et al., 2015); again, with the sample of the latter study being divided into participants with and without a history of interpersonal violence. The stage 1 analysis revealed significant pooled correlations between the treatment condition and anxiety ($\rho_{TY} = -0.10, p = .034$) and between the mediator (combined cognitive variables) and anxiety ($\rho_{MY} = 0.26, p < .001$). The correlation between treatment condition and the mediator was $\rho_{TY} = -0.13$ ($p = .072$). Heterogeneity was considerable ($Q(6) = 26.4$, $p < .001$; I^2 for $\rho_{TM} = 77\%$; I^2 for $\rho_{TY} = 41\%$). The random effects variance for the relation between the mediator (combined cognitive variables) and anxiety (ρ_{MY}) was fixed to zero ($I^2 = 0$), because this was required to ensure convergence of the TSSEM procedure. The second stage of the analysis yielded a significant effect of combined cognitive variables on anxiety (b = 0.251; 95%-CI: [0.128, 0.373]). All other paths as well as the indirect and direct effects were non-significant (a = −0.132; 95%-CI: [−0.276, 0.012]; ab = −0.033; 95%-CI: [−0.082, 0.003]; c' = −0.065; 95%-CI: [−0.162 0.037]; Fig. 4).

Due to an insufficient number of studies per subgroup (less than three), the execution of subgroup analyses was not feasible. Likewise, the conduction of sensitivity analyses was also not feasible, because due to the small number of studies that we could include in the quantitative synthesis.

4. Discussion

To the best of our knowledge, this is the first systematic review and meta-analysis investigating mediators and mechanisms of change in digital interventions for adult anxiety disorders. In a first step, this review summarized and methodologically evaluated trials investigating therapeutic processes in IMIs for anxiety, including 26 studies that examined 64 mediators with 6042 participants overall. Cognitive variables and skills were found to be the most common investigated mediators, with these two categories also evincing the highest percentages of significant mediators across categories. In a second step, TSSEM was conducted wherever feasible. Mediators capturing changes in negative thinking yielded a significant indirect effect, whereas combined cognitive mediators yielded non-significant indirect effects when meta-analyzed. Besides, the limited number of primary studies precluded moderator and sensitivity analyses, restricting further conclusions and highlighting the need for future process research in this field.

Since the concepts, components and operalizations of CBT are especially suited to be conveyed by technologically means (e.g., Ebert et al., 2018), most IMIs in this review were based upon this theoretical underpinning; an expectable finding (Andersson, Carlbring, Titov, & Lindefors, 2019), which mirrors also the evidence base on mediation studies in digital interventions for depression (Domhardt, Steubl, et al., 2021). In accordance with the predominance of internet-based CBT (iCBT), it is not so much astonishing, that the majority of investigated mediators were also of a cognitive nature and relate to this theoretical orientation to a certain extent. Other therapeutic approaches such as ACT, mindfulness-based, problem-solving, behavioral activation, relaxation or psychodynamic orientations were far less researched in IMIs, limiting conclusions about the specificity of mediators to certain theoretical orientations, as well as their potential consistency across therapeutic approaches.

Although 64 mediator variables were examined in primary studies overall, these variables were conceptually different at large and are nested within a rather heterogeneous body of research. The limited overlap and high heterogeneity regarding the investigated mediators suggests that there are currently no "well-established" mediators supported by multiple studies in this field of research. Thus, TSSEM was only feasible for negative thinking and combined cognitive mediators in clinical and non-clinical samples. In most analyses, we found rather high heterogeneity, possibly due to the broad categorization of combined cognitive mediators. Instead, the analysis of negative thinking yielded the lowest indices of heterogeneity of all TSSEM analyses, which might be associated with higher conceptual similarity and instrumental operationalization of the included mediators, also facilitating the scarce significant finding. However, considering that in all three TSSEM analyses approximately one third of underlying effect sizes were missing, the meta-analytical findings need to be viewed very cautiously and considered as preliminary, necessitating further high-quality primary research that enables innovative methodological approaches to synthesize intervening variable effects (Cheung, 2020). Then again, these findings also reflect a diverse and growing field of research still in its infancy, exploring various possible mediators and mechanisms of change in digital interventions for anxiety.

As related to the specific anxiety disorders, study characteristics indicate that mainly GAD was examined in clinical samples, followed by health anxiety and SAD, next to self-reported anxiety symptoms as assessed with the GAD-7 in non-clinical samples. Other anxiety disorders like SP, PD or A were not subject of investigation in any included study, limiting the current body of evidence and precluding inferences about these neglected anxiety disorders widely. While process research about IMIs appears to be rare especially for PD and A, there are already studies substantiating the efficacy of IMIs for PD/A and SP (e.g., Domhardt, Letsch, et al., 2020; Kok, van Straten, Beekman, & Cuijpers, 2014). Thus, the next steps of identifying the therapeutic processes in these anxiety disorders are warranted to complement the evidence base.

In studies investigating mediators and mechanisms of change in face-to-face psychotherapy – identified alongside the primary focus of this review – CBT appears to be the most widely used theoretical underpinning (e.g., Alden, Buhr, Robichaud, Trew, & Plasencia, 2018; King

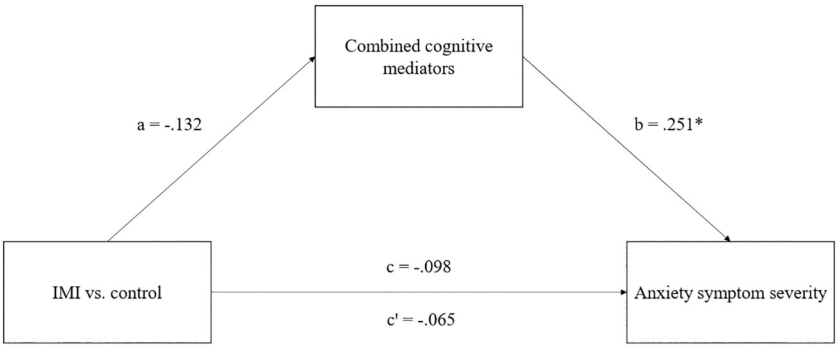


Fig. 4. Path diagram displaying the stage two mediational model of the TSSEM for combined cognitive mediators in non-clinical samples. Values are path coefficients. *Parameter estimates are significantly different from zero (i.e., 95%-CIs do not contain zero).

et al., 2012; Renner, Valentiner, & Holzman, 2017), analogous to process research on digital interventions. Yet, very few mediators were examined in both delivery formats. For example, acceptance (Ștefan, Capraru, & Szilágyi, 2018; Viskovich & Pakenham, 2020) and self-compassion (Ștefan et al., 2018; Schotanus-Dijkstra, Pieterse, Drossaert, Walburg, & Bohlmeijer, 2019) were subject of investigation in both face-to-face psychotherapy and digital interventions for anxiety, revealing significant intervening variable effects; whereas the mediator cost bias revealed mixed findings between delivery types (Possis et al., 2013; Stevenson et al., 2019). Furthermore, in contrast to the predominance of GAD in process research on digital interventions, studies on face-to-face psychotherapy seemed to mostly investigate SAD (e.g., Alden et al., 2018; Goldin et al., 2016; Riccardi, Korte, & Schmidt, 2017) or PD (e.g., Meulenbeek, Spinhoven, Smit, van Balkom, & Cuijpers, 2010; Meuret, Rosenfield, Seidel, Bhaskara, & Hofmann, 2010; Reinecke, Waldenmaier, Cooper, & Harmer, 2013). Moreover, it is also a remarkable finding that in both branches of psychotherapy process research, studies on change mechanisms associated with exposure therapy seem to be underrepresented, as contrasted with the well-established overall importance of exposure and response prevention in psychotherapeutic treatments of anxiety-related disorders (Carl et al., 2019; Foa & McLean, 2016; Hofmann, Asnaani, Vonk, Sawyer, & Fang, 2012).

The assessment of requirements for process research revealed that most primary studies adhered to certain quality criteria adequately (i.e., utilizing an RCT design and control group, providing a theoretical foundation of mediators, recruiting at least 40 participants in each trial group, and appropriate consideration of confounders). Furthermore, the criterion of strong statistical association was fulfilled in the majority of included studies. However, there were also considerable shortcomings regarding the evaluation of temporality and experimental manipulation of the mediator(s), which were the least adhered to criteria. Similar patterns concerning the fulfillment of these criteria have been found in other systematic reviews assessing mediation studies of face-to-face psychotherapy (Lemmens et al., 2016) and digital interventions for depression (Domhardt, Steubl, et al., 2021). Yet, since the establishment of temporality is of principal importance and also the direct experimental manipulation of mediators is largely pending, causal inferences are widely precluded at this point.

The quality rating in the current review revealed three studies which particularly set an example regarding the adherence to preferable standards for process research, since they fulfilled all criteria apart from directly manipulating the mediator variable(s): Heckendorf et al. (2019), Hedman et al. (2013) and Newby et al. (2014). As such, these studies can be regarded as benchmark trials for future high-quality research. Furthermore, the study conducted by Heckendorf et al. (2019) was the only one, explicitly stating evidence for a dose-response relationship between their intervention and the mediator "repetitive negative thinking", therewith addressing the gradient criterion.

The risk of bias assessment yielded a high overall risk of bias in 73.00% of the studies. Yet, this strong tendency towards an overall high risk of bias might be also a result of the novel, more stringent RoB 2 algorithm (Sterne et al., 2019): As soon as at least one category in a specific study is rated to have "some concerns" or "high risk of bias", the overall risk of bias will be considered to have "some concerns" or "high risk", respectively. Because most included studies could not meaningfully conduct masking of participants – largely due to the specific characteristics of (digital) psychotherapy research (Domhardt, Letsch, et al., 2020; Munder & Barth, 2018) – these individuals could have been influenced in their answers. Of note, we rated the risk of bias as "high", if masking of participants was not conducted and the outcome was assessed via self-report, therefore resulting in an overall high risk of bias. Yet, when omitting this criterion and liberalizing the approach of the RoB assessment in this regard (given the constraints of psychotherapy research), the percentage of studies with an high overall risk of bias is reduced to 52%.

Subgroup analyses might have contributed to explain the prevalent heterogeneity in TSSEM by identifying possible moderators (e.g., type of anxiety disorder, therapeutic approach), but were not feasible due to an insufficient number of studies per analysis. Yet, other studies have investigated the role of possible moderating variables in IMIs for anxiety before. For example, evidence was found for the moderators recruitment setting (Romijn et al., 2019) and treatment modality (El Alaoui et al., 2013). Furthermore, Olthuis et al. (2016) identified that type of anxiety disorder and therapist contact time moderated outcomes, but emphasized the preliminary nature of their findings as well. Thus, research on treatment moderators of digital interventions needs to be expanded – ideally within the context of process research (Huibers et al., 2021) – in order to precisely investigate for whom an intervention works and for whom it does not (Kraemer, 2016). Thereby contributing to the optimization of treatment selection in anxiety and informing the implementation of personalized digital treatment options (Cohen & DeRubeis, 2018; Domhardt, Cuijpers, et al., 2021; Donker et al., 2013; Karyotaki et al., 2021; Simon & Perlis, 2010).

4.1. Limitations und strengths

The current systematic review and meta-analysis features several strengths, such as adherence to a pre-registered study protocol, comprehensive search for relevant published and unpublished studies, as well as employing TSSEM for statistical synthesis. Yet, there are also limitations to this review and the current evidence base that contextualize the findings. First, the generalizability of results might be reduced, as almost all studies were conducted in western countries, samples were predominantly female and only English papers were included; also, publication bias cannot be ruled out. Second, an explorative approach was applied in the current review and mediator variables of interest were not specified in advance, in order to enable a comprehensive overview of this rather novel and evolving branch of research. Third, the small number of eligible studies as well as considerable heterogeneity between studies and mediators impaired the statistical analyses, limiting the ability to draw meaningful conclusions from the quantitative analyses. Given the limited empirical evidence base, the meta-analytical findings have to be considered as preliminary and interpreted with caution. Fourth, the risk of bias assessment indicated substantial shortcomings of eligible primary studies, although this finding should be appraised in the context of the typical constraints of psychotherapy research. Further, attrition rates of included studies were rather high on average, which is a common finding in IMIs, especially when they are unguided (e.g., Karyotaki et al., 2015). Lastly, primary studies frequently utilized a WLC, which might have lead to an overestimation of statistical significance and effect sizes, in contrast to comparisons resorting to active controls (Domhardt, Steubl, et al., 2021; Mohr et al., 2009).

4.2. Future directions

In order to advance the field of research on therapeutic processes in digital interventions, the following recommendations might be informative for future studies. Firstly, from a methodological point of view, it is of high relevance to amend the shortcomings concerning the adherence to criteria for process research as outlined in the quality assessment. Furthermore, future studies should aim to be more methodologically rigorous in regard to the a priori publication of a study protocol including a data analysis plan, and the resort of multiple sources on mediators beyond mere self-report. Moreover, prospective studies (also on other mediators than evaluated in this review) should utilize more sophisticated and current methods of mediation analysis and causal inference, such as causal mediation analysis (Imai, Keele, & Tingley, 2010; Mayer et al., 2014), latent growth curve modeling (Cheong, MacKinnon, & Khoo, 2003; von Soest & Hagtvet, 2011), dynamic structural equation modeling (Grimm & Ram, 2018; Iacobucci,

Saldanha, & Deng, 2007), or dynamic network approaches (Hofmann et al., 2020) – suitable to take the temporal order of longitudinal data into account, illustrate the actual patterns of therapeutic change, and ideally are able to model non-linear changes (Laurenceau, Hayes, & Feldman, 2007) and sudden gains (Hedman et al., 2014).

Secondly, since CBT was the most utilized therapeutic underpinning of IMIs, more studies investigating alternative theoretical foundations are required, in order to facilitate analyses on the potentially moderating nature of therapeutic orientations and examine questions of (non-) specificity (Cuijpers, Reijnders, & Huibers, 2019; Domhardt, Steubl, et al., 2021). This applies also for the examined anxiety disorders, since the studies included in our investigation mainly focused on GAD and health anxiety, and evidence-based insights on other anxiety disorders (e.g., PD, A or SP) are urgently needed, in order to inform the development of disorder-specific and transdiagnostic treatment packages alike (Domhardt et al., 2019), tackling common underlying core psychopathological processes (Krueger, 1999).

Thirdly, future studies should report relevant information on mediation analyses more consistently (especially in regard to correlation coefficients and measurement points for mediators and outcomes), enabling more comprehensive meta-analytical syntheses with TSSEM (Cheung, 2020; Cheung & Chan, 2005) or other meta-analytic structural equation modeling (MASEM) approaches (e.g., Cheung, 2019; Cheung, 2020; Jak & Cheung, 2018; Katz, Matanky, Aviram, & Yovel, 2020). Moreover, the potential of novel technological opportunities in psychotherapy process research seems not fully exploited thus far (Domhardt, Cuijpers, et al., 2021). Interestingly, although passive sensing methodologies and digital phenotyping approaches with smartphones (Baumeister & Montag, 2019) might generate insights on behaviors and mechanisms in real-life, behavioral mediators are currently the least examined group of intervening variables thus far. Yet, novel technological approaches might facilitate and extend knowledge derived from passive data as well as from biological variables (Domhardt, Cuijpers, et al., 2021), in addition to the predominant information derived from self-reports and ecological momentary assessment studies found in this review. Likewise, qualitative research approaches directly asking participants about their personal experiences of therapeutic change during (digital) interventions for anxiety may generate new insights, extending the findings by merely replicating the questions posed by prior research efforts.

Additionally, given the rather high attrition rates in eligible primary studies, investigations of how to best increase the engagement of users to the interventions seems key (Graham, Lattie, & Mohr, 2019; Yardley et al., 2016), ensuring that relevant therapeutic processes are induced and behavior changes in daily lives can actually take effect. Also, deterioration rates and adverse events should be more frequently assessed and reported in primary studies (Domhardt, Letsch, et al., 2020), enabling analyses of potential associations between mediators and adverse events (Domhardt, Steubl, et al., 2021), which could subsequently contribute to the secure implementation of digital interventions in mental health care. Finally, due to the high heterogeneity concerning the current evidence base of mediators in IMIs for anxiety disorders, further research examining more (conceptually identical) mediators is required in order to be able to conduct more integrative meta-analytic pooling with TSSEM or other approaches to MASEM, generating precise information on the differential strength and magnitude of specific intervening variable effects. Moreover, meta-analyses relying on individual participant data (e.g., Büscher et al., 2020; Furukawa et al., 2019; Lin et al., 2019; Reins et al., 2020) might allow for advanced methodologies for psychotherapy process research and enable even more fine-grained mediation analyses in the future.

5. Conclusion

The results of this review indicate that predominantly cognitive mediators are investigated in IMIs for anxiety to date, also evincing the second highest proportion of significance after skills; followed by other mediators, with emotional and behavioral variables being the least examined in mediation studies so far. The adherence of primary studies to several quality criteria for process research seems adequate on certain domains; yet, especially the establishment of temporality and experimental manipulation of investigated mediators require more judicious attention in future research. A better observance of these two crucial criteria of mechanism research would allow for more robust causal inferences, which are currently precluded widely. Up to now, the findings of this review provide an overview about the state of research on change mechanisms in IMIs for anxiety and might serve as a guide for future studies, dedicated to expand our knowledge about the ways and processes *how* digital interventions achieve therapeutic change.

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Contributors

MD, HN and HB developed the design of the study. HN and SE conducted the systematic literature searches, extracted the data, and rated the risk of bias and methodological quality criteria of included studies, under the supervision of MD. HN, MD, YT and SG analyzed the data. MD wrote the first draft of the manuscript. All authors (MD, HN, SE, AB, AM, SG, YT and HB) have contributed to the further writing, and have approved the final manuscript.

Declaration of competing interest

All authors declare that they have no conflicts of interest.

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Supplementary data

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Chapter 11

Mediators and mechanisms of change in internet- and mobile-based interventions for depression: A systematic review

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Review



Mediators and mechanisms of change in internet- and mobile-based interventions for depression: A systematic review

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ABSTRACT

The efficacy of Internet- and mobile-based interventions (IMIs) for depression in adults is well established. Yet, comprehensive knowledge on the mediators responsible for therapeutic change in these interventions is pending. Therefore, we conducted the first systematic review on mediators in IMIs for depression, investigating mechanisms of change in interventions with different theoretical backgrounds and delivery modes (PROSPERO CRD42019130301). Two independent reviewers screened references from five databases (i.e., Cochrane Library, Embase, MEDLINE/PubMed, PsycINFO and ICTRP), selected studies for inclusion and extracted data from eligible studies. We included 26 RCTs on mediators in IMIs for depression (6820 participants), rated their risk of bias and adherence to methodological quality criteria for psychotherapy process research. Primary studies examined 64 mediators, with cognitive variables (e.g., perceived control, rumination or interpretation bias) being the largest group of both examined (m = 28) and significant mediators (m = 22); followed by a range of other mediators, including mindfulness, acceptance and behavioral activation. Our findings might contribute to the empirically-informed advancement of interventions and mental health care practices, enabling optimized treatment outcomes for patients with depression. Furthermore, we discuss implications for future research and provide methodological recommendations for forthcoming mediation studies with more pertinent designs, allowing for inferences with higher causal specificity.

1. Introduction

Depression is highly prevalent (Kessler & Bromet, 2013) and associated with substantial personal and societal burden (Vos et al., 2016). Psychotherapeutic interventions with several theoretical backgrounds are effective in treating depressive symptoms, irrespective of whether they are implemented face-to-face (Barth et al., 2013; Cuijpers, Karyotaki, de Wit, & Ebert, 2019) or delivered remotely via the Internet (Cuijpers, Noma, Karyotaki, Cipriani, & Furukawa, 2019; Ebert et al., 2018; Karyotaki et al., 2018) or mobile-based communication technology (Firth et al., 2017; Linardon, Cuijpers, Carlbring, Messer, & Fuller-Tyszkiewicz, 2019). However, far less is known *whereby* and *how* these psychotherapeutic interventions "work" (Cuijpers, Cristea, Karyotaki, Reijnders, & Hollon, 2017; Cuijpers, Reijnders, & Huibers, 2019; Lemmens, Muller, Arntz, & Huibers, 2016), and in which aspects the change mechanisms in interventions with divergent theoretical orientations and delivery modes might differ. Evidence-based knowledge on these issues is important, as it can inform intervention development and mental health care practices (Cuijpers, 2016; Domhardt, Geßlein, von Rezori, & Baumeister, 2019), highlighting ways to more powerful intervention packages with optimized treatment outcomes.

1.1. Mechanisms of change research – Concepts, definitions and methods

Knowledge on the mechanisms of change in psychotherapeutic interventions for depression can be obtained primarily by two research

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approaches, component studies and mediation studies. Component studies aim to determine the influence of single intervention components on treatment efficacy, thereby contributing to the understanding *whereby* therapies work (Cuijpers, Reijnders, & Huibers, 2019; Domhardt et al., 2019). In these studies, multicomponent psychotherapeutic interventions are compared with disentangled variations of the same intervention (Borkovec & Costonguay, 1998) in which either a component is left out (i.e., dismantling studies) or added to the full treatment package (i.e., additive design studies). When these component studies are conducted within a framework of randomized controlled trials (RCTs), they generate strong causal evidence on the incremental (add on) effects of single intervention components (Cuijpers et al., 2017; Domhardt et al., 2019). These components can be consecutively considered as "active ingredients" of therapies and further differentiated into specific or common factors of psychotherapeutic interventions (Mulder, Murray, & Rucklidge, 2017). Specific factors are those therapeutic techniques and procedures that are inherent to a particular therapeutic approach, based on the respective model of psychotherapy and/or delineated from a disorder-specific etiological model (DeRubeis, Brotman, & Gibbons, 2005); examples for specific factors are cognitive restructuring and behavioral activation related to CBT, or defensive and reflective functioning related to psychodynamic therapies. In contrast, common factors are considered to be generally constituent in psychotherapeutic interventions, regardless of their theoretical orientation or specific therapeutic approach (Wampold, 2015); examples for common factors are the working alliance or the induction of expectations or hope. Meanwhile, the long-lasting debate about the relative importance and differential role of specific and common factors seems to shift to the joint notion that both factors – as well as their respective interactions – contribute to treatment effectiveness (Mulder et al., 2017; Tschacher, Junghan, & Pfammatter, 2014).

Nevertheless, insights that are generated with component studies do not necessarily reveal *how* psychotherapeutic interventions work, and which processes within patients lead to therapeutic change. These endeavors are the main purpose of mediation studies (Kazdin, 2007, 2009), which can be regarded as the essence and core approach of psychotherapy process research. Mediators, like self-efficacy (Bandura, 1978) or functional thoughts (Beck, Rush, Shaw, & Emery, 1979), are intervening variables that account statistically for the relationship between a psychotherapeutic intervention and an outcome variable (Kazdin, 2007), and thereby potentially point to mechanisms through which the intervention achieves its effects (Kraemer, Wilson, Fairburn, & Agras, 2002). Yet, it is important to bear in mind that mediators might be congruent and identical to a mechanism (i.e., the actual process responsible for change), but might also be a proxy for one or more other variables that do not explain the hypothesized mechanism (Kazdin, 2007). These proxy variables are either (a) unknown and/or unmeasured, or (b) both known and measured, with subsequent implications for the scope of causal inferences (Ohlsson & Kendler, 2019). Accordingly, in the context of psychotherapy process research it is worthwhile that mediators are deduced theoretically (i.e., conceptually represent a plausible change mechanism that is induced by an intervention component), are defined and operationalized a priori, and are tested against other known potential intervening variables (Johansson & Høglend, 2007; Kazdin, 2007; Kraemer et al., 2002; Laurenceau, Hayes, & Feldman, 2007).

In contrast, moderators are variables and demographic characteristics, like comorbidity or age, that influence the magnitude or direction of the relationship between an intervention and outcome, thereby indicating on whom and under which circumstances treatments have differential effects (Kazdin, 2007; Kraemer et al., 2002). Variables that qualify for moderators must precede an intervention and need to be independent to the intervention (Kraemer, Kiernan, Essex, & Kupfer, 2008); whereas variables that qualify for mediators always come after an intervention (during treatment) and are related to the intervention (Kraemer et al., 2008). As such, moderators suggest that different processes are involved (i.e., "moderated mediation", James & Brett, 1984; Kazdin, 2007), but conceptually represent no mechanisms of therapeutic change themselves (Kraemer et al., 2002; Laurenceau et al., 2007).

To date, the most widely used method to statistically evaluate mediators was introduced by Reuben Baron and David Kenny with their seminal paper in 1986, also known as the causal steps approach. In this approach, four conditions are tested consecutively within a regression framework (Baron & Kenny, 1986), in order to demonstrate that a mediator M transmits the effect of an independent variable X (the intervention) on a dependent variable Y (the outcome). Although the method of Baron and Kenny to mediation analysis is still very prominent in different scientific disciplines, this approach has several limitations that are especially disadvantageous in psychotherapy process research on depression. For instance, as the statistical power associated with the causal steps method is very low (as are type I error rates), large sample sizes and large treatment effects are necessary to be able to detect indirect effects (MacKinnon et al., 2002; MacKinnon, Fairchild, & Fritz, 2007); yet, these are two conditions that are hardly present in psychotherapy process research on depression (Lemmens et al., 2016). Moreover, it is challenging to apply the causal steps method to models with multiple intervening variables and to assess each of the indirect effects independently (MacKinnon et al., 2007); however, it is most likely that several distinct processes are involved in psychotherapeutic interventions for common mental disorders (Cuijpers, Reijnders, & Huibers, 2019; Domhardt et al., 2019), and multi-mediator models should be evaluated accordingly (Kazdin, 2007, 2009). Most importantly, the causal steps method is only applicable when differential treatment effects are available. Considering the common finding that several psychotherapeutic interventions are equally effective in treating depression (e.g., Barth et al., 2013; Cuijpers, Karyotaki, et al., 2019), it is a significant downside that mediation analyses after Baron and Kenny are not practical under these circumstances – while knowledge on whether these equally effective treatments operate with shared or distinct working mechanisms would be of particular importance.

Consequently, recent advancements aimed to alleviate these limitations and strived to develop statistical methods more suitable for psychotherapy research. Most prominently, Helena Kraemer and the MacArthur group proposed a novel framework that builds upon the same logic of the causal steps method, but opened up opportunities to conduct mediation analyses even when no differential treatment effects are observed and/or the statistical power would be too low to detect intervening variable effects with the Baron and Kenny approach (Kraemer et al., 2002; Kraemer et al., 2008; MacKinnon et al., 2007). In the former case, an interaction between the intervention and the mediator is deemed to be sufficient (Kraemer et al., 2002), and in the latter a "joint significance" test is endorsed (MacKinnon et al., 2002); a procedure, in which it is simultaneously tested whether the independent variable is related to the intervening variable and whether the intervening variable is related to the dependent variable (Hollon & DeRubeis, 2009; MacKinnon et al., 2002). Further recent developments and approaches to mediation analyses are comprehensively summarized by Hayes (2018), Hofmann, Curtiss, and Hayes (2020) and MacKinnon (2017).

1.2. Criteria for the detection of causality and implications for study designs

Still, statistical mediation alone is not sufficient to detect mechanisms of change and corroborate causality (i.e., the relation between cause and effect, Gregor, 2006). Several other criteria strengthen the evidence for actual change processes and pave the way toward the determination of causality (Hernán & Robins, 2019; Kazdin, 2007, 2009) – a subject of philosophical debate for more than 2000 years (Kraemer et al., 2008; Ohlsson & Kendler, 2019). Aside the aforementioned criteria of a *theoretical foundation* of plausible processes and the

necessity of a *strong statistical association* (between intervention, mediator and outcome), a basic prerequisite to assume causality is temporal precedence. The essential criterion of *temporality* is met, when a timeline can be established that the intervention leads to changes in the mediator, and the changes in the mediator precede changes in the outcome – and not vice versa (Kazdin, 2007; Kraemer et al., 2008). Hence, only longitudinal study designs with several concurrent assessments of the mediator and outcome variables with at least three measurement points are assumed to be suitable to evaluate this criterion and establish the actual directionality and shape of change (Laurenceau et al., 2007). The criteria of *specificity* (of the association between intervention, mediator and outcome), *gradient* (i.e., dose-response relationship between mediator and outcome) and *consistency* (of results on mediators across studies) can further back the case for causality (Kazdin, 2007, 2009). Moreover, findings are enormously strengthened when they result from an *experimental design*. This can be achieved either by randomly assigning adequate numbers of participants to different comparison conditions in an RCT (Laurenceau et al., 2007), or by directly manipulating the mediator variable itself (Kazdin, 2007). In this latter approach, it is safe to ascertain that the experimental variation of the mediator causally leads to the observed changes in the outcome, whereas in the former approach one can merely assume that the intervention effects are mediated by the purported construct and not by other conceptually differing proxy variables. This is also why the concurrent assessment of *multiple mediators* – as well as multiple outcomes (Laurenceau et al., 2007) – is highly advisable in order to falsify rivalling hypotheses on therapeutic processes (Kazdin, 2007, 2009). Altogether, multiple converging lines of research observant to these criteria and resorting to different methodologies, while addressing the same question (i.e., triangulation; Munafò & Davey Smith, 2018), are necessary to approximate specific mechanisms of change and prove causality (Kazdin, 2007, 2009; Ohlsson & Kendler, 2019).

However, it is also to acknowledge that the criteria of *specificity*, *gradient* and *consistency* are not absolute, and several important exemptions to these arguments need to be considered. For instance, it might be that different treatment modalities, such as CBT or pharmacotherapy, operate with shared and/or distinct processes, on the same and/or differing levels of action (e.g., behavioral activation vs. alterations in neurotransmission; Hollon, 2019). And these shared (e.g., modifying distorted cognitions) or distinct mechanisms might further happen simultaneously and/or consecutively during treatment, might be independent to another or influence each other dynamically (Hofmann et al., 2020). It is thus central to differentiate between non-specificity in causal processes and actual non-causality, as well as to consider possible differential associations between interventions and mediators on the one hand, and mediators and outcomes on the other hand (Hollon, DeRubeis, & Evans, 1987). Furthermore, the association of a mediator with an outcome might be linear and therefore imply a gradient, but might be also in another multifaceted relation (e.g., U- or S-shaped) that does not concur with a dose-response relationship (Hofmann et al., 2020; Laurenceau et al., 2007). These examples illustrate that the findings on mediators and mechanisms of change must not be necessarily consistent, but might even differ considerably between studies, owing to the complexities of human behavior change.

1.3. Evidence for mediators and mechanisms of change in psychotherapeutic interventions for depression

The evidence base on mediators in face-to-face psychotherapies for depression derived from systematic reviews indicates that intervention effects are mediated by a range of cognitive, behavioral and emotional processes, as well as by the acquirement and usage of different skills (Lemmens et al., 2016). The majority of studies investigated numerous cognitive mediators like dysfunctional thinking (Cristea et al., 2015) or cognitive changes in general (Lorenzo-Luaces, German, & DeRubeis, 2015), and provide some support to the theorized cognitive processes of CBT and its third wave variant Acceptance and Commitment Therapy (ACT; Stockton et al., 2019) to this point. Furthermore, some specific cognitive processes of psychodynamic therapies like changes in insight (Johansson et al., 2010) and self-understanding (Leichsenring, Steinert, & Crits-Christoph, 2018) are documented in samples with mixed diagnoses so far. Besides, behavioral activation has been shown to represent a relevant factor in the treatment of depression (Baumeister, 2017; Jacobson et al., 1996; Richards et al., 2016) and might unfold its effects by decreasing avoidance behavior, as well as increasing positive experiences and reward (Hopko, Ryba, McIndoo, & File, 2016). In addition, some emotional processes (Lemmens et al., 2016) are found to be therapeutic when addressed with different emotion-regulation strategies, like reappraisal, changes in rumination or problem-solving (Aldao, Nolen-Hoeksema, & Schweizer, 2010). In line with the training and growth aspect of evidence-based psychotherapies, the acquisition and usage of mindfulness skills (van der Velden et al., 2015), interpersonal skills (Lipsitz & Markowitz, 2013) and problem-solving skills (Malouff, Thorsteinsson, & Schutte, 2007) are all found to be significant mediators in psychotherapies for depression (Lemmens et al., 2016). Overall, only few mediation studies in these reviews met all quality criteria for process research at once, largely precluding causal inferences so far.

In contrast to the evidence base on face-to-face psychotherapies, the knowledge on the mediators in technology-delivered psychotherapeutic interventions for depression is even more fragmented and limited. To date, there is only one single narrative review on mediators in Internet-based and computerized CBT for depression (Mogoase, Cobeanu, David, Giosan, & Szentagotai, 2017), ignoring mobile-based interventions and neglecting therapeutic approaches beyond CBT. This gap in the literature is a significant drawback, as both Internet- and mobile-based interventions (IMIs) possess the potential to complement and augment existing psychotherapeutic services for depression (Firth et al., 2017; Karyotaki et al., 2017; Karyotaki, Ebert, et al., 2018), considering their particular features and presumed advantages, like flexibility and anonymity in conduct, possible cost-effectiveness and scalability on a population scale. In these ways, digital health interventions are thought to contribute to the mitigation of the disease burden associated with depression substantially (Buntrock et al., 2016; Domhardt, Steubl, & Baumeister, 2018; Ebert, Cuijpers, Muñoz, & Baumeister, 2017; Karyotaki et al., 2017; Karyotaki, Ebert, et al., 2018; Königbauer, Letsch, Doebler, Ebert, & Baumeister, 2017).

1.4. The current study

Accordingly, specific knowledge on the mechanisms of change in guided (with accompanying human support) and unguided (without support) IMIs for depression is of high relevance, in order to build their distinct evidence base respective to their theoretical foundation, contributing to enhanced intervention development and informing the implementation of IMIs in routine clinical care. Furthermore, IMIs convey novel technological and methodological opportunities for psychotherapy research into change mechanisms that might not only disclose the active ingredients of IMIs themselves, but ancillary also contribute to unravel the processes in face-to-face interventions. This is because IMIs allow for a higher standardization of interventions, as prior confounds of psychotherapy research like treatment fidelity (i.e., the actual presentation of therapeutic content) or therapist factors (e.g., professional experience, personal views) can be hold constant, and intervention components can be clearly and reliably operationalized (Domhardt et al., 2019; Furukawa et al., 2019; Steubl, Sachser, Baumeister, & Domhardt, 2019). Hence, IMIs enable an unprecedented way to break down the utterly complex processes of psychotherapeutic interventions into paradigmatic fragments and allow for the evaluation of specific mechanisms of therapeutic change in original experimental designs (Domhardt et al., minor revision). In addition, studies with IMIs might facilitate the attainment of sample sizes sufficient to detect small, but clinically relevant intervening variable effects, as participants can be

recruited on large scale and interventions can be implemented irrespective of the constraints of space and time. Research exploiting these possibilities might thereby contribute to a better understanding to which degree technology-delivered and face-to-face psychotherapeutic interventions operate with shared and/or distinct processes; and disclose, if there are actually specific digital components, as well as unique mediators and mechanisms of change in IMIs for depression.

Considering these novel opportunities and acknowledging the fast growing field of digital health research (Andersson, Titov, Dear, Rozental, & Carlbring, 2019), it seems both timely and worthwhile to provide the first comprehensive systematic overview on mechanisms of change in IMIs for depression. As such, with this study we aimed to systematically review and methodologically assess studies that reported on mediators in various forms of IMIs for depression in adults, informing psychotherapy process research, intervention development and the implementation of IMIs in routine care alike.

2. Method

This systematic review was conducted in line with the recommendations of the Cochrane Collaboration (Higgins & Green, 2011) and is reported in accordance to the PRISMA statement (Moher, Liberati, Tetzlaff, & Altman, 2009). Further detailed information on the design and methodology of this study can be found within the protocol at PROSPERO (CRD42019130301).

2.1. Eligibility criteria and search strategy

In this review we included (a) RCTs, in which (b) a guided or unguided IMI for depression (of various theoretical backgrounds) was compared to (c) an active or non-active control group, (d) in adults (≥18 years) (e) with symptoms of depression based on self-report or diagnostic interview. Eligible studies had to report (f) depression symptom severity as outcome and (g) examine at least one mediator variable by means of statistical mediation analysis (all approaches that qualify for mediation analyses were eligible). Studies with (h) non-clinical samples (i.e., depression symptoms were assessed without applying a clinical cut-off score) were eligible as well, but are reported separately. Studies with (i) an experimental manipulation of mediator variables were also included. Studies had to be (j) written in English, had obtained ethical approval, and (k) were published in a peer-reviewed journal, or (l) indexed "with preliminary/unpublished results" in the International Clinical Trials Registry Platform (ICTRP). Overall, with the application of these inclusion criteria, we intended to enable a comprehensive overview of this branch of research, allowing for comparisons between studies with "clinical" and "non-clinical" samples, as well as between interventions with divergent theoretical underpinnings and delivery modes.

The search strategy was threefold. First, the electronic databases Cochrane Library (CENTRAL), Embase, MEDLINE/PubMed and PsycINFO were systematically searched with a predefined set of search strings in Ovid, from database inception to September 1, 2019. Second, the ICTRP was consulted to detect studies with preliminary or unpublished results. Third, the reference lists of all eligible studies were searched by hand, to identify other relevant studies.

The combinations of index, MESH and free terms were indicative for "Depression", "Internet", "Mobile", "Psychotherapy", "Intervention", "Mediators" and "Mechanisms". The full list of search strings, as well as the search strategies for each database can be found in the Appendix (Tables A.1, A.2).

2.2. Study selection and data extraction

Study selection and data extraction were conducted independently by two researchers (MD and LS). Disagreements were solved by discussion. Titles and abstracts were screened, and irrelevant records were discarded. The full texts of remaining references were retrieved, and assessed according to the aforementioned inclusion criteria.

The following data were extracted from eligible studies: (a) study identification items, (b) sample characteristics, (c) comparison groups, (d) number of participants, (e) mean age, (f) drop-out and intervention adherence, (g) number of modules and intervention duration, (h) post-treatment and follow-up, (i) measures of depression symptom severity, (j) potential mediators (with instruments and measurement points), and (k) statistical methods for mediation analyses, as well as (l) clinical outcomes.

2.3. Risk of bias assessment and evaluation of methodological quality for process research

To determine the risk of bias and methodological quality of included studies, two rating systems were applied independently by two reviewers (MD and LS), with disagreements solved by discussion. First, the Cochrane Collaboration's tool for assessing risk of bias (Higgins et al., 2011) was deployed on all papers on all seven criteria (i.e., "random sequence generation", "allocation concealment", "blinding of participants and personnel", "blinding of outcome assessment", "incomplete outcome data", "selective reporting", and "other bias"), as having either "low", "unclear" or "high risk of bias".

Second, in order to evaluate the appropriateness of research designs of included studies to detect mechanisms of change and to approach causality, a rating system based on the criteria proposed by Alan Kazdin (2007, 2009) and adapted to psychotherapy research for depression by Lemmens et al. (2016) was applied. Each study was rated on the following criteria as either fulfilled ("+") or not fulfilled ("-"): (a) RCT, (b) control group, (c) theoretical foundation, (d) minimal threshold for sample size per group ($n \geq 40$), (e) concurrent examination of multiple mediators, (f) evaluation of temporality (i.e., three or more longitudinal assessments of mediators and outcome variables), and (g) direct experimental manipulation of a mediator. In contrast to Lemmens et al. (2016), the criterion of theoretical foundation of mediators was deployed additionally in the rating system. In line with Lemmens et al. (2016), three aspects originally suggested by Kazdin (2007) were not incorporated in the rating system, as they are either not meaningfully applicable in single studies (consistency) or might be too exclusive for certain mechanisms (gradient and specificity). Nevertheless, these issues are addressed in the discussion.

Since our primary intention was to assess the methodological quality of included studies and to guide this novel branch of process research conceptually, we did not plan to meta-analytically evaluate mediators within this review (PROSPERO CRD42019130301). A theoretically-deduced framework on the mechanisms of change in IMIs for depression will be reported elsewhere (Domhardt et al., in preparation).

3. Results

3.1. Study characteristics

The systematic searches for mediation studies yielded in 3255 initial hits; after the removal of duplicates and title and abstract screening, 58 articles were assessed in full text review with reasons for exclusion outlined in a PRISMA flow chart (Fig. 1). Finally, a total of 26 RCTs met the eligibility criteria and were included in this review. Half of these studies examined samples with clinically depressed patients ($n = 2769$) (Choi et al., 2014; Clarke et al., 2014; Forand et al., 2018; Hirsch et al., 2018; Lamers et al., 2015; Newby, Williams, & Andrews, 2014; Pictet, Jermann, & Ceschi, 2016; Pots, Trompetter, Schreurs, & Bohlmeijer, 2016; Seeley et al., 2019; Terides et al., 2017; van der Zanden, Galindo-Garre, Curie, Kramer, & Cuijpers, 2014; Warmerdam, van Straten, Jongsma, Twisk, & Cuijpers, 2010; Williams, Blackwell, Mackenzie, Holmes, & Andrews, 2013); whereas the other 13 studies focused on samples in which depression symptoms were assessed without applying

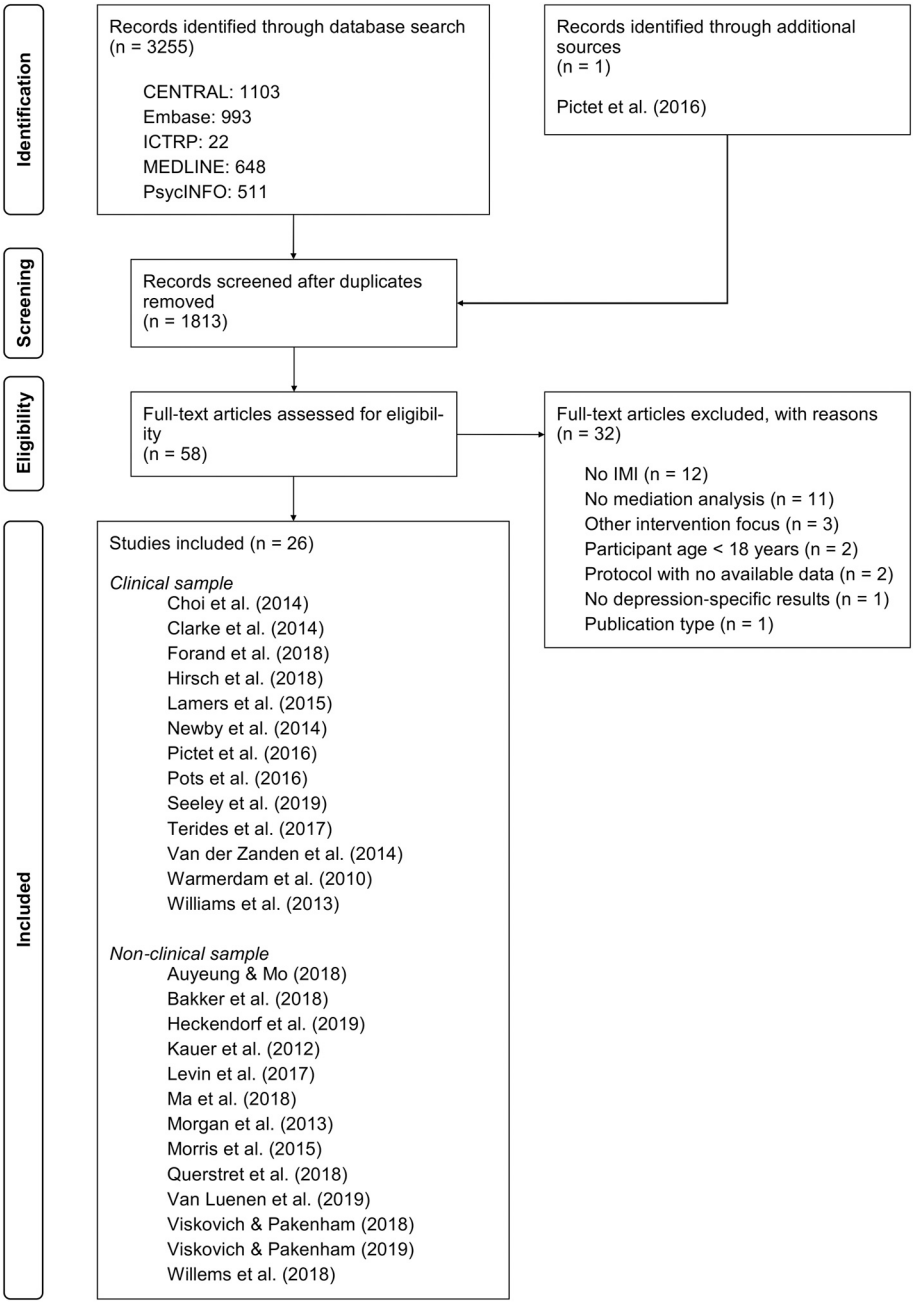


Fig. 1. PRISMA flow chart.

a clinical cut-off score (i.e., "non-clinical"), comprising mixed samples with other physical and mental impairments, or without pathology (n = 4051) (Auyeung & Mo, 2018; Bakker, Kazantzis, Rickwood, & Rickard, 2018; Heckendorf, Lehr, Ebert, & Freund, 2019; Kauer et al., 2012; Levin, Haeger, Pierce, & Twohig, 2017; Ma, She, Siu, Zeng, & Liu, 2018; Morgan, Mackinnon, & Jorm, 2013; Morris, Schueller, & Picard, 2015; Querstret, Cropley, & Fife-Schaw, 2018; van Luenen, Kraaij, Spinhoven, Wilderjans, & Garnefski, 2019; Viskovich & Pakenham, 2018; Viskovich & Pakenham, 2019; Willems et al., 2017). Table 1 provides a detailed overview on study characteristics and extracted data.

Most studies were conducted in western countries (92.3%; i.e., 34.6% Australia, 23.1% the Netherlands, 19.2% the USA, 7.7% the United Kingdom, 3.8% Germany, and 3.8% Switzerland; vs. 7.7% China) and were published within the past five years (2014–2019; 84.6%). The majority of studies (k = 18 studies; 69.2%) had recruited participants via (online) advertisements. Other recruitment settings included (online) clinics (k = 3; 11.5%), agencies or specialized centers (k = 2; 7.7%), and general practitioners (k = 2; 7.7%), as well as an established waitlist (k = 1; 3.8%). The mean ages of participants across studies ranged from 18.7 to 64.8 years (M = 36.6; SD = 12.3), and almost three-fourths of included participants were female (73.3%; range: 12% to 100%). Sample sizes ranged between 69 and 1162 participants, with a mean sample size of 262 participants (SD = 243). In total, 6820 participants were included in this review.

Internet-based interventions were evaluated in 21 studies (80.8%) and mobile-based interventions were examined in two studies (7.7%). Other studies investigated an intervention combining Internet- and mobile-components (k = 2; 7.7%) or psychotherapy via Internet-based video calls (k = 1; 3.8%). The most frequently researched theoretical background of IMIs was CBT (k = 8; 30.8%), followed by ACT (k = 4; 15.4%), Mindfulness Based Cognitive Therapy (MBCT; k = 2; 7.7%) and Positive Psychology (k = 2; 7.7%). Further underpinnings of IMIs

Table 1
Study Characteristics.

Authors (Year); Country	Sample / recruitment strategy	Comparison groups	Number of participants per group (% females)	Mean age (SD)	Study drop-out[#]	Mean number of modules completed / time spent	Percentages of participants completing all modules	Modules (no.) / duration in weeks*	Post-treatment; follow-up (s) in weeks*	Depression symptom severity instruments	Potential mediators	Mediator instruments (measurement points in weeks*)	Statistical method for mediation analyses (authors)
Clinical samples													
Choi et al. (2014); US	Homebound older adults with depressive symptoms / aging-service agencies	Tele-PST vs. in-person PST vs. telephone care calls	56 63 39 (79%)	64.8 (9.18)	12%	–	–	6/–	12; 24, 36	HAMD	↓ Disability status	WHODAS II (0, 12, 24, 36)	Latent growth curve mediation modelling within a framework of SEM (Cheong et al., 2003; MacKinnon, 2008)
Clarke et al. (2014)[a]; AUS	Self-reported mild-to-moderate symptoms of depression, anxiety and stress / internet, radio, print	Mobile phone and web intervention vs. attention control condition vs. WLC	242 248 230 (70%)	38.9 (–)	28%[a]	1.6 modules[a] / 14.7 log-ins[a] / 49 self-monitor entries[a]	–	12[a]/7	8; –	DASS (depress. subscale)	↑ Self-efficacy (n.s.)	MHSES (0, 8)	Mixed models repeated measures (Baron & Kenny, 1986) and revised version of the Sobel Test (Preacher & Hayes, 2004)
Forand et al. (2018); US	Self-reported depressive symptoms / online, flyers, newspapers, referral	Guided iCBT vs. WLC	60 30 (75%)	33 (–)	24%	6.22 sessions / -	56%	8/8	8; –	PHQ-9 (primary outcome); HAMD	↑ Cognitive skills ↑ Behavioral activation (n.s.)	CCTS-SR (0, 3, 8) BADS-SF (0, 3, 8)	PROCESS (Hayes, 2013)
Hirsch et al. (2018); UK	Diagnosed generalized anxiety disorder or depression (SCID) / online, newspapers, university e-mails	Standard CBM vs. CBM with prior RNT vs. active control	44** 43** 44** (82%)	29.9 (11.19)	16%	–	74%	10/4	4; 4	PHQ-9	↓ Negative interpretation bias (approached significance: $p = .054$) ↓ Negative interpretation bias (n.s.)	SST (0, 4, 8) RT (0, 4, 8)	SEM (product of coefficients approach; Iacobucci et al., 2007)
Lamers et al. (2015); NL	Self-reported mild to moderate depressive symptoms / online, newspaper	Guided life-review vs. guided expressive writing vs. WLC	58 58 58 (77%)	56.9 (9.15)	10%	- / 5.25 h peer week - / 2.29 h peer week	75.9% 79.3%	7/10	13; 26, 52	CES-D	↑ Ego-integrity ↓Rumination	Northwestern Ego-Integrity scale (0, 13, 26, 52) Ruminative Response Scale (0, 13, 26, 52)	Stepwise regression analyses and bootstrapping (Preacher & Hayes, 2004)
Newby et al. (2014); AUS	Self-reported and diagnosed (MINI) MDD, GAD or both / waitlist, online	Guided iCBT vs. WLC	46 53 (78%)	44 (12.2)	3%	–	89%	6/10	10; 13	PHQ-9	↓ Repetitive negative thinking (RNT) ↓ Positive metacognitive	RTQ (0, 4–10***, 10, 13) PBRS-A (0, 4–10***, 10, 13)	PROCESS (Hayes, 2013)

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Table 1 (*continued*)

Authors (Year); Country	Sample / recruitment strategy	Comparison groups	Number of participants per group (% females)	Mean age (SD)	Study drop-out[#]	Mean number of modules completed / time spent	Percentages of participants completing all modules	Modules (no.) / duration in weeks*	Post-treatment; follow-up (s) in weeks*	Depression symptom severity instruments	Potential mediators	Mediator instruments (measurement points in weeks*)	Statistical method for mediation analyses (authors)
											beliefs about RNT		
Pictet et al. (2016); CH	Self-reported depressive symptoms / flyers, online	Imagery CBM vs. control CBM vs. WLC	34 34 33 (79%)	26.7 (9.14)	4%	–	97% 94%	4/1	1; 3	BDI-II	↓ Depression-related interpretation bias	AST-D-II (0,1,3)	PROCESS (Hayes, 2012)
Pots et al. (2016)[b]; NL	Self-reported mild to moderate depressive symptoms (& MINI) / newspapers, online	Web-based ACT vs. online expressive writing vs. WLC	82 67 87 (76%)	46.9 (12.06)	16%	–	73%[b] 63%[b]	9/9–12	13; 26, 52	CES-D	↑ Psycholog. flexibility ↑ Mindfulness facets	AAQ-II (0, 13, 26, 52) FFMQ-SF (0, 13, 26, 52)	PROCESS (Hayes, 2013)
Seeley et al. (2019); US	Mothers with elevated depressive symptoms (CES—D; PHQ-8) / Head Start centers	Trial 1: Guided iCBT (+ MI) vs. delayed intervention / facilitated TAU	70	31.0 (6.4)	1%	6.4 sessions / 15.1 h	-	8/8	14	BDI-II (Trial 1)	↑ Behavioral activation[c] ↓ Negative thoughts[c] ↑ Savoring of pleasant events[c]	BADS (0, 14/26) ATQ (0, 14/26) PASPO (0, 14/26)	Mplus (Muthén & Muthén, 1998-2012); bootstrapping (MacKinnon et al., 2004)
		Trial 2: Guided iCBT (+ MI) vs. MI and referral to services	266 (100%)	31.8 (7.2)	11%	6.6 sessions / 5.5 h	-		26	PHQ-9 (Trial 2)			
Terides et al. (2017); AUS	Self-reported clinically mild symptoms of anxiety (GAD-7), depression (PHQ-9), or both (MINI) / seeking online treatment	iCBT vs. WLC	68[d] 80[d] (81%)	44.7 (12.75)	14%	–	63%	5/8	8; 13	PHQ-9	↑ CBT skills usage (cognitive restructuring, rewarding behaviors[d], and activity scheduling)	FATS (0, 8, 13; both groups) FATS (0, 1, 2, 3, 4, 5, 6, 7, 8, 13; only iCBT group)	PROCESS (Hayes, 2013)
van der Zanden et al. (2014)[e]; NL	Young adults with self-reported depressive symptoms / adds in GP offices, institutions, online	iCBT group course vs. WLC	121 123 (84%)	20.9 (2.2)	20%	3.2 sessions / -	20%[e]	6/6	12; 24	CES-D	↑ Mastery ↓ Anxiety	Mastery Scale (0, 12, 24) HADS-A (0, 12, 24)	Path analysis mediation models in Mplus (Baron & Kenny, 1986; MacKinnon, 2008; Muthén & Muthén, 1998-2012)

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Table 1 (*continued*)

Authors (Year); Country	Sample / recruitment strategy	Comparison groups	Number of participants per group (% females)	Mean age (SD)	Study drop-out#	Mean number of modules completed / time spent	Percentages of participants completing all modules	Modules (no.) / duration in weeks*	Post-treatment; follow-up (s) in weeks*	Depression symptom severity instruments	Potential mediators	Mediator instruments (measurement points in weeks*)	Statistical method for mediation analyses (authors)
Warmerdam et al. (2010); NL	Self-reported depressive symptoms / adds in newspapers, online	Guided iCBT vs. guided online PST vs. WLC	88 88 87 (71%)	45 (12.1)	34%	–	38.6% 37.5%	8/8 5/5	5, 8; –	CES-D	↓ Dysfunct. attitudes ↓ Worrying ↑Perceived control ↓ Negative problem orientation ↑ Positive problem orientation (n.s.) ↑ Rational problem orientation (n.s) ↓ Avoidance (n. s.) ↓ Impulsivity/ carelessness (n. s.)	DAS (0, 5, 8) PSWQ (0, 5, 8) Mastery Scale (0, 5, 8) SPSI-R (0, 5, 8) SPSI-R (0, 5, 8) SPSI-R (0, 5, 8) SPSI-R (0, 5, 8) SPSI-R (0, 5, 8)	Linear mixed modelling (Baron & Kenny, 1986)
Williams et al. (2013); AUS	Diagnosed major depressive episode (MINI) / research unit	CBM-I (7-day) + iCBT (10-week) vs. WLC	38 31 (76%)	44.8 (12.05)	39%	–	50%	13/11	11; –	BDI-II	↑ Change in interpretation bias	AST-D (0,1) SST (0, 1)	PROCESS (Hayes, 2012)
Non-clinical samples													
Auyeung and Mo (2018); CN	University students / mail, social media	Online PPI vs. writing group	70 69 (73%)	22.8 (3.78)	28%	4.48 / -	57% (≥ 5 sessions)	6/	1; –	CESD-10	↑ Sense of autonomy ↑ Positive affects (n.s.)	Subscale of BPNSFS (0, 1) Subscale of PANAS (0, 1)	Latent variable SEM approach (Russel et al., 1998)
Bakker et al. (2018); AUS	Community sample / social media	CBT toolkit app vs. mood tracking app vs. CBT strategy app vs. WLC	78 78 78 78 (81%)	34.2 (12.1)	55%	–	36% (imputed 30-day)	–/4	4; –	PHQ-9	↑ Coping self-efficacy ↑ Emotional self-awareness (n.s.) ↑ Mental health literacy (n.s.)	CSES (0, 4) ESAS-R (0, 4) Mental Health Literacy Questionnaire (0, 4)	PROCESS (Hayes, 2013)
Heckendorf et al. (2019); GER	Community sample / online news magazine	Internet- and app-based gratitude intervention vs. WLC	132 130 (59%)	42.4 (10.9)	20%	3.5 / 4.0 weeks	53.8%	5 / 5	6; 13, 26	CES-D	↓ Repetitive negative thinking	PTQ (0, 6, 13, 26)	Parallel multiple mediation analyses (Hayes and Rockwood, 2017)

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Table 1 (*continued*)

Authors (Year); Country	Sample / recruitment strategy	Comparison groups	Number of participants per group (% females)	Mean age (SD)	Study drop-out#	Mean number of modules completed / time spent	Percentages of participants completing all modules	Modules (no.) / duration in weeks*	Post-treatment; follow-up (s) in weeks*	Depression symptom severity instruments	Potential mediators	Mediator instruments (measurement points in weeks*)	Statistical method for mediation analyses (authors)
Kauer et al. (2012); AUS	Young people with mild or severe emotional or mental health concerns / GPs	Monitoring of 8 areas of functioning vs. attention control group	69 49 (72%)	18.7 (3.2)	26%	3.3 entries per day / 17.7 days completed 4 entries per day / 16.8 days completed	56% (minimum dose) 53% (minimum dose)	−/2–4	2–4; 6	DASS	↑ Emotional self-awareness	ESA Scale (0, 2–4, 6)	Parallel process latent growth curve modelling in Mplus (Cheong et al., 2003; Muthén & Muthén, 1998-2012)
Levin et al. (2017); US	College students in distress / online, institutions, flyers	Web-based ACT vs. WLC	40 39 (66%)	20.5 (2.73)	22%	–	55%	6/4	4; –	CCAPS-34	↑ Mindful acceptance ↓ Obstruction to valued living	VQ (0, 4) PHLMS (0, 4)	Cross product of coefficient test in Mplus (Muthén & Muthén, 1998-2012)
Ma et al. (2018); CN	Adults aiming to reduce stress / web-based adds	Group mindfulness-based intervention vs. self-directed mindfulness-based intervention vs. discussion group vs. WLC	48 48 48 48 (58%)	27.8 (7.98)	60%	–	–	8/8	8; –	SDS	↑ Emotion regulation	DERS (0, 8)	PROCESS (Preacher & Hayes, 2008)
Morgan et al. (2013); AUS	Individuals with subthreshold depression / web-based sources (adds etc.)	E-mails promoting self-help strategies vs. non-directive depression information	568 (79%)	36.3 (13.8)	–	–	–	12/6	6; –	PHQ-9	↑ Use of self-help strategies	Frequency of strategy use (5-category scale; 0, 6)	MEDIATE (Preacher & Hayes, 2008)
Morris et al. (2015); US	Young adults / universities, online, social media	Web-based cognitive reappraisal program vs. online expressive writing	135 130 (72%)	23.7 (5.3)	37%	21 log-ins / 9 min 18 s per session (1013.28 words) 10 log-ins / 3 min 10 s per session (433.85 words)	–	−/3	3; –	CES-D	↑ Reappraisal	ERQ (0,3)	SPSS macro (Preacher & Hayes, 2008)
Querstret et al. (2018); UK	Community / institutions, online, social media	Online mindfulness intervention vs. WLC	60 58 (81%)	40.7 (10.45)	31%	–	75% (completed intervention in <12 weeks)	−/4	4; 13, 26	PHQ-9	↑ Non-judging ↑ Describing (n. s.) ↑ Acting with awareness (n.s.)	FFMQ-SF (0, 4)	PROCESS (Hayes, 2013)

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Table 1 (*continued*)

Authors (Year); Country	Sample / recruitment strategy	Comparison groups	Number of participants per group (% females)	Mean age (SD)	Study drop-out#	Mean number of modules completed / time spent	Percentages of participants completing all modules	Modules (no.) / duration in weeks*	Post-treatment; follow-up (s) in weeks*	Depression symptom severity instruments	Potential mediators	Mediator instruments (measurement points in weeks*)	Statistical method for mediation analyses (authors)
van Luenen et al. (2019); NL	People with HIV and depressive symptoms / HIV treatment centers	iCBT intervention vs. attention-only WLC	97 91 (12%)	46.3 (10.63)	19%	–	–	8 / 8	8; –	PHQ-2	↑ Activation ↑ Relaxation (n.s.) ↓ Catastrophizing (n.s.) ↑ Positive refocusing (n.s.) ↑ Goal re-engagement ↑ Coping self-efficacy (n.s.)	BADS (0, 1, 3, 5, 8) Self-designed item CERQ-short (0, 1, 3, 5, 8) CERQ-short (0, 1, 3, 5, 8) GDGRS (0, 1, 3, 5, 8) Two self-designed items (0, 1, 2, 5, 8)	Multilevel SEM, exploratory analyses, and autoregressive latent trajectory analysis (Bollen & Curran, 2004; Garland et al., 2015; Preacher et al., 2010)
Viskovich and Pakenham (2018); AUS	University students / institutions, social media, flyers	ACT with recommendation vs. ACT with no recommendation vs. ACT with stepped approach and enforced gaps	40 43 47 (75%)	26.3 (7.96)	61%	–	27%	4/4	4; –	DASS-SF	↑ Acceptance ↑ Education values ratio ↑ Valued living ↑ Mindfulness (n.s.) ↑ Cognitive fusion (n.s.)	AAQ-II (0, 4) Engaged Living Scale (0, 4) Subscale of Personal Values Questionnaire II (0,4) Mindful Attention Awareness Scale (0, 4) Cognitive Fusion Questionnaire (0,4)	MEMORE (Montoya & Hayes, 2016)
Viskovich and Pakenham (2019); AUS	University students / social media, institutions, e-mail	Web-based ACT vs. WLC	596 566 (68%)	26.9 (8.77)	42%	–	34% (started or completed module 4)	4 / 4	4; 12	DASS-SF	↑ Acceptance ↑ Cognitive Fusion ↑ Valued living ↑ Present moment awareness ↑ Education values ratio	AAQ-II (0, 4, 12) Cognitive Fusion Questionnaire (0, 4, 12) Engaged Living Scale (0, 4, 12) Mindful Attention Awareness Scale (0, 4, 12) Subscale of Personal Values Questionnaire II (0, 4, 12)	PROCESS and MEMORE (Montoya & Hayes, 2017; Preacher & Hayes, 2004)

(*continued on next page*)

Table 1 (*continued*)

Authors (Year); Country	Sample / recruitment strategy	Comparison groups	Number of participants per group (% females)	Mean age (SD)	Study drop-out[#]	Mean number of modules completed / time spent	Percentages of participants completing all modules	Modules (no.) / duration in weeks*	Post-treatment; follow-up (s) in weeks*	Depression symptom severity instruments	Potential mediators	Mediator instruments (measurement points in weeks*)	Statistical method for mediation analyses (authors)
Willems et al. (2017); NL	Cancer survivors / hospitals	Stand-alone online intervention vs. WLC	265 253 (81%)	56.3 (11.17)	18%	2.22 modules / -	8.5% (≥5 modules)	8/–	-; 26	HADS-D	↑ Perceived personal control over cancer ↑ Problem-solving skills (n. s.)	Personal control subscale of IPQ-R (0, 13, 26) SPSI-R (0, 13, 26)	Product-of-coefficients approach with PROCESS (MacKinnon, 2008; Hayes, 2013; Preacher & Hayes, 2008)

Note. AAQ-II = Acceptance and Action Questionnaire-II (Bond et al., 2011); ACT = Acceptance and Commitment Therapy; AST-D = Ambiguous Scenarios Test – Depression (Berna, Lang, Goodwin, & Holmes, 2011); AST-D-II = Ambiguous Scenarios Test for depression-related bias-II (Rohrbacher & Reinecke, 2014); ATQ = Automatic Thoughts Questionnaire (Hollon & Kendall, 1980); AUS = Australia; BADS = Behavioral Activation for Depression Scale (Kanter, Mulick, Busch, Berlin, & Martell, 2007); BADS-SF = Behavioral Activation for Depression Scale – Short Form (Manos, Kanter, & Luo, 2011); BDI-II = Becks Depression Inventory, revised (Beck et al., 1996); BPNSFS = Psychological Need Satisfaction and Frustration Scale (Chen et al., 2014); CBM = Cognitive Bias Modification; CBM-I = imagery-based Cognitive-Bias Modification; CCAPS-34 = Counseling Center Assessment of Psychological Symptoms-34 (Locke et al., 2012); CCTS-SR = Competencies of Cognitive Therapy Scale – Self-Report (Strunk, Hollars, Adler, Goldstein, & Braun, 2014); CERQ-short = Cognitive Emotion Regulation Questionnaire short version (Garnefski & Kraaij, 2006); CES-D = Center of Epidemiological Studies-Depression scale (Radloff, 1977); CESD-10 = Centre for Epidemiologic Studies Depression Scale – Shortened Version (Andresen et al., 1994); Cognitive Fusion Questionnaire (Gillanders et al., 2014); CH = Confoederatio Helvetica/Switzerland; CN = People's Republic of China; CSES = Coping Self-Efficacy Scale (Chesney et al., 2006); DAS = Dysfunctional Attitudes Scale (Weismann, 1979); DASS(-SF) = Depression Anxiety Stress Scale (-Short Form; Lovibond & Lovibond, 1995); DERS = Difficulties in Emotion Regulation Scale (Gratz & Roemer, 2004); Engaged Living Scale (Trompetter et al., 2013); ERQ = Emotion Regulation Questionnaire (Gross & John, 2003); ESA Scale = adapted from 20-item Self-reflection and Insight Scale (Grant, Franklin, & Langford, 2002), 10-item Ruminative Response Scale (Treynor, Gonzalez, & Nolen-Hoeksema, 2003) and 12-item Meta-Evaluation Scale (Mayer & Stevens, 1994); ESAS-R = Emotional Self-Awareness Scale – Revised (Bakker & Rickard, 2018); FFMQ-SF = Five Facet Mindfulness Questionnaire – Short Form (Baer et al., 2006); FATS = Frequency of Actions and Thoughts Scale (Terides et al., 2016); GAD = Generalized Anxiety Disorder; GAD-7 = generalized anxiety disorder screener (Löwe et al., 2008); GP = General Practitioner; (HADS-A = Hospital Anxiety and Depression scale-Anxiety (Zigmond & Snaith, 1983); GDGRS = Goal Disengagement and Goal Re-engagement Scale (Wrosch et al., 2003); HADS-D = Hospital Anxiety and Depression scale-Depression (Zigmond & Snaith, 1983); HAMD = Hamilton Rating Scale for Depression (Hamilton, 1960); iCBT = internet-based Cognitive-Behavioral Therapy; IPQ-R = Illness perception questionnaire - revised (Moss-Morris et al., 2002); Mastery Scale (Pearlin & Schooler, 1978); MDD = Major Depressive Disorder; Mental Health Literacy Questionnaire (Bakker & Rickard, 2017; 2018); MHSES = Mental Health Self-efficacy Scale (Clarke et al., 2014); MI = motivational interviewing; Mindful Attention Awareness Scale (Brown & Ryan, 2003); MINI = Mini International Neuropsychiatric Interview (Sheehan et al., 1998); NL = the Netherlands; Northwestern Ego-Integrity scale (Janis et al., unpublished); PANAS = Positive and Negative Affect Schedule (Watson et al., 1988); PASPO = Perceived Ability to Savor Positive Outcomes (Bryant, 1989); PBRS-A = Positive Beliefs about Rumination Scale-Adapted Version (Watkins & Moulds, 2005); PHLMS = Philadelphia Mindfulness Scale (Cardaciotto et al., 2008); PHQ-9 = Patient Health Questionnaire depression scale (Kroenke et al., 2001); PHQ-2 = first two questions of PHQ-9; Personal Values Questionnaire II (Blackledge, Ciarrochi, & Bailey, n.d.); PPI = Positive Psychology Intervention; PST = Problem-solving therapy; PSWQ = Penn State Worry Questionnaire (Meyer et al., 1990); PTQ = Perseverative Thinking Questionnaire (Ehring et al., 2011); RNT = Repetitive negative thinking; RTQ = Repetitive Thinking Questionnaire (McEvoy et al., 2010); RT = Recognition Test (based on Mathews & Mackintosh, 2000); Ruminative Response Scale (Roelofs, Muris, Huibers, Peeters, & Arntz, 2006); SCID = Structured Clinical Interview for DSM-5 (First, Williams, Karg, & Spitzer, 2015); SD = Standard Deviation; SDS = Self-Rating Depression Scale (Zung, 1965); SEM = Structural Equation Modelling; SPSI-R = Social Problem-Solving Inventory-Revised (D'Zurilla, Chang, Nottingham, & Faccini, 1998); SST = Scrambled Sentences Test (Rude et al.,2002; Wenzlaff & Bates, 1998; Wenzlaff & Bates, 2000); TAU = treatment as usual; UK = United Kingdom; US = United States of America; VQ = Valuing Questionnaire (Smout et al., 2014); WHODAS II = World Health Organization Disability Assessment Schedule II (WHO, 2000); WLC = Waiting List Control.

[a] Information were also retrieved from the initial RCT (Proudfoot et al., 2013); [b] Information were also retrieved from the initial RCT (Pots et al., 2016); [c] Results were reported for multiple mediation models and were consistent in both trials in Seeley et al. (2018). The two trials in Seeley et al. (2018) were treated as separate investigations of mediators, as they were conducted with different samples and different outcome measurements for depression, although the same mediator instruments were deployed in both trials; [d] In the study of Terides et al. (2017), mediation analyses were conducted with complete outcome data only, whereas information in regard to completers differed (flow chart: iCBT: $n = 65$; WLC: $n = 75$; Table 5: iCBT: $n = 55$; WLC: $n = 66$). Although the results of mediation analyses in Table 5 in Terides et al. (2017) indicate that rewarding behavior was evaluated as a significant mediator, the authors discuss these significant findings in the discussion section conversely; [e] Information were also retrieved from the initial RCT (van der Zanden et al., 2012); [#] Study drop out was calculated as follows: participants completing posttreatment assessment divided by randomized participants across groups. These calculations are not necessarily in accordance with the study drop-out rates as reported in primary studies; * Conversions were conducted as follows (rounded off to whole numbers): 1 day = 0.14 weeks, 1 month = 4.35 weeks, 1 year = 52.18 weeks; ** Analyzed sample; *** Participants in Newby et al. (2014) received mid-treatment measurement prior to commencing lesson 4, which was available 4 weeks after baseline; – Not reported/applicable; ↑ Increasing scores in the mediator construct were hypothesized to be associated with depressive symptom improvement; ↓ Decreasing scores in the mediator constructs were hypothesized to be associated with depressive symptom improvement; (n.s.) not significant.

Table 2
Quality assessment for process research.

Authors (Year)	RCT	Control	Theoretical foundation	n ≥ 40 per group	Multiple mediators	Temporality	Manipulation of mediators	Number of criteria met
Clinical samples								
Choi et al. (2014)	+	+	+	−	+	−*	−	4
Clarke et al. (2014)	+	+	+	+	−	−	−	4
Forand et al. (2018)	+	+	+	−	+	+	−	5
Hirsch et al. (2018)	+	+	+	+	−	−*	+	5
Lamers et al. (2015)	+	+	+	+	+	−*	−	5
Newby et al. (2014)	+	+	+	+	+	+	−	6
Pictet et al. (2016)	+	+	+	−	−	−*	−	3
Pots et al. (2016)	+	+	+	+	+	−*	−	5
Seeley et al. (2019)	+	+	+	+[a]	+	−	−	5
Terides et al. (2017)	+	+	+	+	+	−*	−	5
van der Zanden et al. (2014)	+	+	+	+	+	−*	−	5
Warmerdam et al. (2010)	+	+	+	+	+	+	−	6
Williams et al. (2013)	+	+	+	−	−	−	−	3
Non-clinical samples								
Auyeung and Mo (2018)	+	+	+	+	+	−	−	5
Bakker et al. (2018)	+	+	+	+	+	−	−	5
Heckendorf et al. (2019)	+	+	+	+	−	−	−	4
Kauer et al. (2012)	+	+	+	+	−	−	−	4
Levin et al. (2017)	+	+	−	−	+	−	−	3
Ma et al. (2018)	+	+	+	+	−	−	−	4
Morgan et al. (2013)	+	+	+	+	−	−	−	4
Morris et al. (2015)	+	+	+	+	−	−	−	4
Querstret et al. (2018)	+	+	+	+	+	−	−	5
van Luenen et al. (2019)	+	+	+	+	+	+	−	6
Viskovich and Pakenham (2018)	+	+	+	+	+	−	−	5
Viskovich and Pakenham (2019)	+	+	+	+	+	−	−	5
Willems et al. (2017)	+	+	+	+	+	+	−	6

Note. + = requirement met; − = requirement not met. * In these studies the mediator and/or the outcome instruments were deployed on more than two assessment points (including follow-up), but the actual evaluation on temporality (i.e., the mediator changed before the outcome) was not conducted or reported. [a] When evaluating this criterion, the sample sizes of both trials in the study of Seeley et al. (2019) were pooled.

examined in one study each (3.8%) were Cognitive Bias Modification (CBM), Problem-Solving Therapy (PST), interpretation training, life-review, mental health self-efficacy, monitoring, and self-help strategies for behavior change. Three studies (11.5%) included a combined treatment of Internet-based CBT (iCBT) augmented with either CBM, PST or monitoring. Just over half of the studies evaluated unguided IMIs (k = 14; 53.8%), whereas in 12 studies (46.2%) some type of guidance was evaluated. The number of modules in IMIs ranged from 4 to 13 (M = 7.41; SD = 2.59). Study drop-out rates ranged from 1% to 61%.

Wait-list control groups (WLC) were deployed in ten studies (38.5%), while further eight studies (30.8%) added one (or more) other control condition(s) to the WLC. Other comparison groups comprised different active control conditions like an alternative IMI (k = 6; 23.1%), online writing (k = 4; 15.4%), attention control (k = 4; 15.4%), face-to-face psychotherapy (k = 1; 3.8%), motivational interviewing and discussion group (k = 1; 3.8%), non-directive information (k = 1; 3.8%), treatment-as-usual (TAU; k = 1; 3.8%) or referral to other treatment (k = 1; 3.8%).

Frequently utilized instruments to measure depression symptom severity were the Patient Health Questionnaire (PHQ-9 or PHQ-2; Kroenke, Spitzer, & Williams, 2001; k = 9; 34.6%), or the Center of Epidemiological Studies - Depression scale (CES-D; Radloff, 1977) and its shortened version (CES-D-10; Andresen, Malmgren, Carter, & Patrick, 1994; k = 7; 26.9%). The remaining studies deployed the Depression Anxiety Stress Scale and its short form (DASS(-SF); Lovibond & Lovibond, 1995; k = 4; 15.4%), the Beck Depression Inventory (second edition, BDI-II; Beck, Steer, & Brown, 1996; k = 3; 11.5%), the Counseling Center Assessment of Psychological Symptoms (CCAPS-34; Locke et al., 2012; k = 1; 3.8%), the Hamilton Rating Scale for Depression (HAMD; Hamilton, 1960; k = 1; 3.8%), the Hospital Anxiety and Depression Scale - Depression (HADS-D; Zigmond & Snaith, 1983; k = 1; 3.8%) or the Self-Rating Depression Scale (SDS; Zung, 1965; k = 1; 3.8%). As such, with 96.2% (k = 25) the vast majority of included studies used self-report measures to assess depression symptom severity and only one study resorted to a clinician-administered scale.

Mediation analyses were most often conducted by means of bootstrapping procedures (Hayes, 2012; Montoya & Hayes, 2017; Preacher & Hayes, 2008; k = 15; 57.7%) or structural equation modelling (Cheong, MacKinnon, & Khoo, 2003; Iacobucci, Saldanha, & Deng, 2007; MacKinnon, 2017; Muthén & Muthén, 1998-2012; Russell, Kahn, Spoth, & Altmaier, 1998; k = 8; 30.8%). Other approaches to mediation analyses deployed in one study each (3.8%) were linear mixed modelling, mixed models repeated measures and parallel multiple mediation analyses, all within the framework of the causal steps approach (Baron & Kenny, 1986).

3.2. Mediators

Overall, the included studies examined 64 distinct potential mediators (Table 1), of which the majority (m = 42; 65.6%) was found to be significant (Table A.3 in the Appendix). Intervening variables with mixed findings (evaluated both as significant and non-significant) are indicated with the symbol "~". Mediators that were examined in studies that evaluated the temporality criterion are indexed with the letter "t", and mediators that were directly manipulated in an experiment with the letter "e". Due to the wide spectrum and limited overlap of single mediator constructs (i.e., small number of studies per mediator), meta-analytical pooling would not have been feasible.

3.2.1. Cognitive mediators

Cognitive mediators represent the largest group of investigated mediators (m = 28 mediators; 43.7%). In studies with clinical samples the

following mediators were established as significant: cognitive skills[t], positive beliefs, functional metacognitive beliefs, psychological flexibility[~], mastery/perceived control[t], as well as changes in interpretation bias[~,e], rumination, repetitive negative thinking, negative thoughts, dysfunctional attitudes[t] and worrying[t]. In non-clinical samples the cognitive variables coping self-efficacy, valued living, reappraisal, cognitive fusion, perceived control and changes in repetitive negative thinking were established as significant. A total of seven cognitive mediators were found to be non-significant (Table 1).

3.2.2. Behavioral mediators

Findings on behavioral activation (m = 4; 6.3%) were mixed. Behavioral activation[~] was evaluated twice as significant and once as non-significant in studies with clinical samples. In one study resorting to a non-clinical sample, behavioral activation[t] significantly mediated intervention effects (Table 1).

3.2.3. Emotional and affective mediators

Emotional and affective mediators were examined in non-clinical samples only (m = 4; 6.3%). Emotion regulation was evaluated as significant in one study; whereas the findings on emotional self-awareness[~] were mixed, and on positive affect non-significant (Table 1).

3.2.4. Skills as mediators

A total of 18 different skills (m = 18; 28.1%) were examined and these intervening variables comprise the second largest group of mediators. In clinical samples the skills of mindfulness (observing and non-judging of inner experience), CBT skills usage and changes in negative problem orientation[t] were found to be significant; whereas four skills were evaluated as non-significant (Table 1). In non-clinical samples, acceptance, self-help strategies, mindfulness[~] (non-judging and acting with awareness), present moment awareness and problem-solving skills[t] were significant intervening variables; further three skills were found to be non-significant (Table 1).

3.2.5. Other mediating variables

Mediator variables that were not clearly classifiable into one of the aforementioned categories represent the third largest group of mediators (m = 10; 15.6%). In studies with clinical samples, conceptually differing mediators like ego integrity, savoring of pleasant events, disability status, or anxiety were found to be significant. In non-clinical samples the intervening variables sense of autonomy, goal re-engagement[t] and education values were evaluated as significant. Only mental health literacy was evaluated as non-significant in this group of mediators (Table 1).

3.3. Risk of bias and quality assessment for process research

The results of the risk of bias assessment are detailed in Fig. A.1 in the Appendix. The domains with the lowest risk of bias across studies were "selective reporting" and "other bias"; whereas the criterion least met was "blinding of participants and personnel". Of note, masking of participants and therapists is somewhat impossible to accomplish in conventional psychotherapy research, but might be generally possible in IMIs, especially in unguided interventions with two active comparison conditions (Domhardt et al., 2020). Overall, the quality of included studies can be regarded as rather high, with 20 studies (76.9%) having low or moderate risk of bias.

The results of the quality assessment for process research (i.e., evaluation of the causal specificity of studies investigating hypothesized mechanisms) are detailed for each study in Table 2. Obviously, as the criteria *RCT* and *control group* were simultaneously inclusion criteria of this review, all studies adequately adhered to these standards. The next best fulfilled criteria were *theoretical foundation* (k = 25; 96.2% of studies) and *sample size* per group (k = 21; 80.8%). *Multiple mediator variables* were measured in 16 studies (61.5%). Notably, only five studies (19.2%) assessed the mediator and outcome variables at least on three measurement points (*temporality*) and only one single study realized a *direct manipulation of a mediator* in an experimental design (3.8%). In fact, Hirsch et al. (2018) investigated the effects of experimentally inducing positive interpretations prior to cognitive bias modification training (CBM) by means of a priming task. Thereby the authors found that changes in interpretation bias at post-treatment partially mediated the effects of CBM on worry, rumination and anxiety at follow-up in participants with symptoms of depression or anxiety; whereas the intervening variable effect of interpretation bias on depression symptoms missed statistical significance marginally in this experiment (Hirsch et al., 2018).

Altogether, with 16 studies fulfilling five or more (out of seven) quality criteria, the overall study quality based on this rating system can be considered as rather good. An overview of the percentages of studies meeting each quality criterion is outlined in Table A.4, the number of quality criteria met by each study is illustrated in Fig. A.2 across studies (Appendix).

4. Discussion

To our knowledge, this is the first comprehensive systematic review that evaluated mediation studies in various forms of IMIs for depression. In this review, a total of 26 mediation studies with 6820 participants were included, which investigated 64 intervening variables in IMIs based on 11 different theoretical foundations. Thereby, cognitive variables were found to be the largest group of significant mediators. The next largest groups comprised a range of different behavioral and emotional mediators, as well as mindfulness and other skills. Eligible mediation studies were assessed in terms of design characteristics suitable for the convergence of causality, indicating a rather high overall study quality, with still substantial room for improvement on certain aspects within this branch of process research.

As the majority of IMIs were based on CBT-principles, it is not surprising that the majority of examined mediators are somehow related to the conceptualizations of this therapeutic orientation (Beck et al., 1979). Thereby, the cognitive and behavioral mediators examined in IMIs largely correspond to those intervening variables summarized in systematic reviews of face-to-face therapies for depression in general (Lemmens et al., 2016) and cognitive (behavioral) therapy in particular (Cristea et al., 2015; Garratt, Ingram, Rand, & Sawalani, 2007; Hofmann, Asmundson, & Beck, 2013; Kazantzis et al., 2018; Lorenzo-Luaces et al., 2015). These findings indicate that certain cognitive and behavioral processes are consistent in psychotherapeutic interventions for depression, regardless if they are implemented face-to-face or remotely via the Internet or mobile devices. Furthermore, comparisons for cognitive mediators suggest, that these intervening variables might not be specific to C(*B*)T, but may well depict common underlying cognitive processes in psychotherapeutic interventions for depression in general (Hollon et al., 1987; Lorenzo-Luaces et al., 2015; Powers, de Kleine, & Smits, 2017). Yet, more information on specific cognitive processes and mediators not derived from CBT are needed to substantiate these findings, as knowledge from other evidence-based face-to-face psychotherapies for depression (e.g., psychodynamic, client-centered or interpersonal therapy) are largely pending in IMIs so far.

The recency of technology-delivered interventions for depression might have further influenced the findings that processes related to ACT and mindfulness are somewhat more frequently and disproportionately examined in IMIs, when compared to the evidence in face-to-face therapies (Lemmens et al., 2016). The mediators acceptance and mindfulness seem to be specific to these relatively novel therapeutic approaches, although these early indications need to be further substantiated by research directly addressing the specificity of these intervening variables. Moreover, apart from mobile-based monitoring of emotions and areas of functioning (i.e., "tracking"; Bakker et al., 2018; Kauer et al., 2012), no "*digital factors*" (Domhardt et al., minor revision), unique

mediators or specific mechanisms to digitalized interventions for depression were identified to this point. With the concept of "*digital factors*", we refer to factors that are either common to all, or only specific to certain digital health interventions – but are essentially not a component of conventional psychotherapies on-site (Domhardt et al., minor revision). Conceivable "*common digital factors*" are for example the technological implementation, digital working alliance or positive outcome expectations about the digital device and intervention. Presumed "*digital specific factors*" inherent solely to certain interventions may be for instance mobile and passive sensing, continuous automated feedback with smartphones or wearables, as well as real time triggered interventions based on moment-to-moment analyses of human behaviors in everyday life. Upcoming research efforts must clarify, which of these digital factors are indeed active ingredients of technology-delivered interventions, and if they initiate the same or different mechanisms of change when compared to conventional face-to-face psychotherapies. These investigations may also contribute to find effective ways how to best increase adherence rates and the engagement of patients to digital interventions (Yardley et al., 2016), which are especially low when IMIs are unguided and transferred from controlled research settings into routine health care (Domhardt et al., 2019; Graham, Lattie, & Mohr, 2019).

Table 3
Recommendations for intervention development, clinical practice and future research.

Intervention development
- Studies on mediators in mobile-based interventions are scarce; these interventions need to be evaluated in RCTs and their specific processes examined in detail
- Use additional approaches to identify the active ingredients and change mechanisms of IMIs, e.g., component studies, multiphase optimization strategy frameworks using fractional factorial designs, parametric and catalytic RCTs
- Take recent expansions of psychotherapy research into account, since transdiagnostic protocols and process-oriented interventions might further contribute to the scalability of IMIs for depression and common mental disorders
- Further advancements of theories on working mechanisms can inform intervention development

Clinical practice
- Secure that evidence-based components are implemented, which induce established mediators and mechanisms of change essential for improved outcomes (see Table 1 and Table A.3 for (non-)significant mediators)
- Monitor processes in routine clinical care, also those related to possible negative effects and deterioration rates
- Resort to multi-modal assessments (cognitive, behavioral, emotional/affective and/or physiological/biological variables) from multiple sources (e.g., self-report, clinician ratings, passive data), with well-established, but also novel mediator instruments with sound psychometric properties
- Digital phenotyping, i.e., active and passive data collection with smartphones in situ, and ecological momentary assessment studies might provide novel insights on (*digital*) factors and change mechanisms in routine care and daily lives of patients

Future research
- Adhere to methodological recommendations for process research, especially in regard to the establishment of temporality and direct manipulation of mediators (see Table 2 and Table A.3 for details)
- Investigate presumed novel *digital* factors and specific mechanisms in IMIs for depression, as well as mediators not researched so far (e.g., perceived support, distancing, hopefulness, empowerment, attributional style)
- Examine processes associated with negative effects and deterioration rates
- Stick to established conceptual considerations, and evaluate multiple potential mediators that can falsify rivalling theories
- Ponder on the timing of measurements (e.g., early and sudden gains might necessitate measurements early in treatment) and implement fine-grained temporal designs; ideally on a session-by-session basis, and also in daily life between sessions
- Analyze moderators and subgroups, as well as trajectories of change in individual patients
- Use recent statistical methods for mediation analysis (e.g., time lagged mediation analysis or latent growth curve modelling) and evaluate the specific influence of each mediator, as well as their interactions and associations with specific and common factors
- Extend the evidence-base by means of the replication of mediation studies, but also with original component studies, in order to identify the active ingredients of IMIs for depression

Presumably the particular dynamics of Internet intervention research will take up these gaps, and apprehend to recent developments and considerations of psychotherapy research, like the tendency toward a process orientation (Hayes et al., 2019; Hayes, Hofmann, & Ciarrochi, 2020; Hofmann & Hayes, 2019) or the expansions of transdiagnostic protocols to common mental disorders as well (Steele et al., 2018; Weisel et al., 2019). These current developments might also further contribute to the potential of IMIs to expand and augment existing mental health care services (Domhardt et al., 2019; Ebert et al., 2017), by means of scalable self-help interventions (Buntrock et al., 2016; Karyotaki et al., 2017), advanced models of stepped care (Domhardt & Baumeister, 2018; van Straten, Hill, Richards, & Cuijpers, 2015) and blended therapy approaches (Baumeister, Grässle, Ebert, & Krämer, 2018; Domhardt, Steubl, & Baumeister, 2018; Erbe, Eichert, Riper, & Ebert, 2017), as well as by providing tailored interventions for underserved populations (Andersson et al., 2019; Domhardt, Steubl, & Baumeister, 2018). Investigations of transdiagnostic, process-based and tailored interventions in future mediation studies are of particular importance, to comprehensively assess the actual capability of IMIs to extend mental health services within different models of care – for depressive and other common mental disorders alike.

The quality assessment of mediation studies in this review revealed that the majority of included studies adequately adhered to standards of psychotherapy research in general (RCT design, control group), and to some extent also for process research in particular (theoretical deduction of mediators a priori). Still, it is crucial that forthcoming studies stick to established constructs of psychotherapy process research, as outlined in the introduction and overcome persistent conceptual confusions, which ancillary obstructed the debate between proponents of common and specific factors (Mulder et al., 2017). Moreover, the quality assessment of mediation studies indicated some significant shortcomings in their aptness for the detection of change mechanisms and the determination of causality. Most importantly, only a minority of studies (19%) established the temporal ordering of changes in mediators and outcomes with at least three measurement points and were therefore principally able to determine the directionality and shape of change. Yet, the criterion of temporality is considered to be of paramount importance (Kazdin, 2007, 2009), and the establishment of the timeline that changes in the mediator occur before changes in the outcome, represents the Achilles' heel of process research in face-to-face therapies (Kazdin & Nock, 2003) and in IMIs for depression alike. Furthermore, direct causal conclusions are largely precluded also because only one study directly manipulated a mediator variable in an experimental design so far (Hirsch et al., 2018). On the contrary, it is a remarkable strength of the majority of included mediation studies that they were capable to implement relatively large sample sizes per condition, and tested multiple concurrent mediators in order to falsify rivalling mechanisms. The comparatively large sample sizes on average ($M = 262$; $SD = 243$) might have also contributed to the finding that studies using an active comparison group similarly often established significance for examined mediators as studies deploying passive control conditions (59.1% vs. 65.9%). In contrast, the differences in significance on mediators in face-to-face psychotherapies (Lemmens et al., 2016) were markedly more pronounced in studies deploying active controls compared to passive controls (41.3% vs. 69.9%), presumably also partly due to smaller samples sizes ($M = 173$; $SD = 145$) in conventional psychotherapy process research. Noteworthy, the quality of eligible studies did not differ between studies with clinical (61/91 sum score of quality criteria met over studies) and non-clinical samples (60/91) in the current review at hand. Overall, the findings of the quality assessment suggest a rather stable quality in this novel branch of psychotherapy process research in the last five years, also when compared to mediation studies in face-to-face psychotherapies for depression (Lemmens et al., 2016).

Two of four benchmark studies (i.e., fulfilling all quality criteria apart from direct manipulation of mediators; Table 2) illustrate the

aptitude of IMIs to reveal novel insights into presumed change mechanisms. For example, van Luenen et al. (2019) revealed intervening variable effects for behavioral activation and goal re-engagement in Internet-based CBT for 188 participants with HIV on depressive symptoms when compared to WLC. In deploying bivariate autoregressive latent trajectory analysis (Bollen & Curran, 2004), the authors were able to show that the intervening variable effects were stronger for behavioral activation than for goal re-engagement, therewith providing information on the differential magnitude of mediating effects. In another benchmark study, Warmerdam et al. (2010) found in an RCT with 263 clinically depressed participants, that the positive effects of Internet-based CBT and PST on symptom severity were transmitted by the examined mediators in both interventions alike. Therewith, the study disclosed initial evidence that both interventions might operate with shared processes (i.e., changes in dysfunctional attitudes, worrying, negative problem orientation and perceived control), although mediators were conceptually related only to one of the aforementioned theoretical orientations. Aside these findings on (non-)specificity the authors were not able to establish the temporality criterion, even though three measurements of mediators and outcomes were implemented. This was because most symptom change happened early in treatment, not allowing for the detection of later changes in mediators and outcomes after mid-treatment (week five), impeding conclusions on the direction of change. Notably, only one study found initial support for a dose-response relationship between the intervention and the mediator, and explicitly addressed the gradient criterion. In fact, Heckendorf et al. (2019) found that increased usage of the examined gratitude app with daily exercises correlated with the mediator repetitive negative thinking in a community sample of 260 adults compared to WLC on depression and anxiety symptom severity.

4.1. Limitations and strengths

This systematic review offers several strengths, including adherence to a pre-registered study protocol, comprehensive incorporation of IMIs with various theoretical foundations and treatment formats, as well as the relatively high overall quality of eligible studies. However, some important limitations need to be considered when interpreting the findings of the present study. First, the generalizability of this review might be limited, since the vast majority of mediation studies were conducted in western countries and resorted to female participants. Second, the majority of mediation studies used self-report instruments to assess depression outcomes and mediators alike; while this might represent on one side a constraint in terms of the validity and reliability of the assessment of depression symptom severity, the recourse to self-reports might be otherwise an advantage in regard to the detection of change mechanisms, as certain processes are only detectable by introspection of patients. Third, most mediation studies focused on a significance criterion when evaluating the intervening variable effects, but the emphasis on *p*-values might be misleading and the resort to interpretable effect sizes with estimates of accuracy more appropriate (Kraemer, 2019). Fourth, the concentration on statistical significance and the focus on English language publications might have also resulted in some degree of publication bias (Egger et al., 1997; Rothstein, Sutton, & Borenstein, 2005), whereas our systematic searches revealed no relevant non-English papers, and our searches in ICTRP indicated no unpublished registered mediation studies with non-significant findings to this point.

4.2. Future directions

Recommendations for future research on change mechanisms in IMIs for depression, intervention development and clinical practice are summarized in Table 3. Most importantly, forthcoming mediation studies should aim to amend the methodological limitations outlined in the quality assessment, in order to enable inferences with higher causal specificity. Furthermore, future studies should resort to more recent and elaborated approaches to statistical mediation analysis, like dynamic structural equation modelling (Grimm & Ram, 2018; Iacobucci et al., 2007), time lagged mediation analysis (Cole & Maxwell, 2003), latent growth curve modelling (Cheong et al., 2003; von Soest & Hagtvet, 2011) or dynamic network approaches (Hofmann et al., 2020), circumventing the limitations inherent to the causal steps approach, and capable to model the temporal ordering, as well as the actual shape of change. In these ways, the investigation of putative mediators derived from theoretical orientations other than CBT, and the establishment of mediators in mobile-based interventions are of value to enlarge the evidence base and clarify questions of (non-)specificity. Mediators not examined so far (e.g., biological variables, attributional style or social support; Domhardt, Münzer, Fegert, & Goldbeck, 2015), and mediators associated with presumed *digital specific* and *digital common factors* (Domhardt et al., minor revision), like empowerment or self-efficacy, might be of particular relevance for future intervention development, striving for IMIs with higher adherence rates and improved treatment outcomes. Complementary to these research efforts might be the application of the Multiphase Optimization Strategy (MOST; Collins, Murphy, & Strecher, 2007) and methodological advancements to analyze the differential efficacy of intervention components and mediators by innovative meta-analyses of individual participant data (e.g., Furukawa et al., 2019; Lin et al., 2019).

In addition, although mediation studies on IMIs for children and adolescents were not a decisive focus of the present review, our systematic searches revealed only two studies dedicated solely to this younger age group (Riley, Duke, Freeman, Hood, & Harris, 2015; Smith et al., 2015). This shortage of research is a substantial drawback, since empirical findings from adults with depressive disorders should not be conveyed on pediatric populations offhand; given substantial differences in treatment manuals and the consistently lower effect sizes of psychotherapies for depression in children and adolescents, irrespective if interventions are delivered face-to-face (Cuijpers et al., 2020) or technology-mediated (Domhardt, Ebert, & Baumeister, 2018; Ebert et al., 2015). Accurate evidence-based knowledge on the specific mechanisms of change in IMIs for depression in children and adolescents would be of tremendous importance, in order to inform intervention development and increase – the currently rather unsatisfying – effect sizes of psychotherapeutic programs for youth. This is even more relevant, as the utilization rates of conventional evidence-based psychotherapies are low in children and adolescents (Costello, He, Sampson, Kessler, & Merikangas, 2014; Merikangas et al., 2011), and novel digital interventions might be an auspicious opportunity to extend mental health care services, considering that technology-transmitted interventions might be particularly attractive, accessible and scalable for youth.

Finally, as all included studies in this review focused on depression symptom severity as (primary) outcome, upcoming studies should examine the change mechanisms associated with other relevant outcome domains from the patient's perspective, like personal targets, quality of life or negative outcomes to be avoided (Cuijpers, 2019). So far, the relation of mediator variables to negative effects were not obtainable in eligible studies. While crucial evidence on the potential negative effects (Rozental, Boettcher, Andersson, Schmidt, & Carlbring, 2015) and deterioration rates in IMIs for depression are available elsewhere (Ebert et al., 2016; Karyotaki et al., 2018) – indicating no substantial differences between IMIs and face-to-face psychotherapies to date – upcoming studies should investigate the association of mediators to potential adverse outcomes carefully. Comprehensive evidence on these issues would contribute to the safety of technology-delivered interventions for depression, and inform the implementation of guided and unguided IMIs into routine clinical care.

5. Conclusion

Overall, this systematic review indicates that the well-established treatment effects of IMIs for depression are mediated by a range of primarily cognitive variables and skills, as well as several other behavioral and emotional variables, which are comparable to those mediators already identified in face-to-face psychotherapies. However, strong causal conclusions are not warranted to this point, because most often the central criterion of temporality is not established in mediation studies, and experimental studies with a direct manipulation of presumed mediators are largely pending. The findings and methodological recommendations of this review might guide future research, aiming to ascertain the active ingredients and mechanisms of change in technology-delivered interventions for depression, with greater clarity, scientific rigor and higher causal certainty.

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Contributors

MD, PC and HB developed the design of the study. MD and LS conducted the systematic literature searches, extracted the data, and rated the risk of bias and methodological quality criteria of included studies. MD wrote the first draft of the manuscript. All authors (MD, LS, JB, CB, EK, DDE, PC, and HB) have contributed to the further writing, and have approved the final manuscript.

Declaration of Competing Interest

All authors declare that they have no conflicts of interest.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.cpr.2020.101953.

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Part VI

General discussion

General discussion

While the efficacy of digital interventions for a range of mental disorders in different age groups is established, several important research questions in digital mental health are unsettled to date. First and foremost, empirically supported comprehensive insights on the active ingredients and change processes of these interventions are largely lacking. Yet, knowledge *whereby* and *how* digital interventions work is essential to further improve interventions and substantiate the dissemination of digital mental health interventions in routine care. Furthermore, little is known about the actual potential of digital interventions to improve mental health in several specific patient populations, and how digitalized research approaches may contribute to the advancement of psychotherapy process research. Moreover, a cohesive theoretical framework on the mechanisms of change in digital interventions is pending, and innovations in evidence synthesis for mediational studies are needed to precisely estimate the effects of distinct therapeutic processes. As such, the overarching aim of this dissertation is to improve the knowledge on the active ingredients and mechanisms of change in digital interventions for CMD across the lifespan. At that, a series of studies were conducted, with a particular focus on systematic reviews and meta-analyses (comprising findings from 256 RCTs with 33,607 participants), in order to pursue the specific research questions accurately and generate the most informative evidence. In this closing part, the results of this thesis are summarized and interpreted within the context of what is already known. In addition, the implications of the findings are discussed, the methodological limitations of the studies are considered, and pathways for future research as well as conclusions across studies are provided.

Key findings

Efficacy, effectiveness, and quality of digital interventions for CMD across the lifespan

Meta-analytical evidence documents that digital interventions are both efficacious and effective for a range of common mental disorders and age groups. This applies for example for adults with depression (Königbauer et al., 2017; Moshe et al., 2021; Reins et al., 2021), anxiety (Olthuis et al., 2016; Romijn et al., 2019) or PTSD (Kuester et al., 2016; Steubl et al., 2021). However, for some specific patient and age groups important clinically relevant

research questions concerning the efficacy (i.e., do interventions work in highly controlled laboratory settings?) and effectiveness (i.e., do they also work under real-world conditions in routine care?) of interventions remained unresolved so far. The present dissertation added to the current evidence base in answering some of these questions.

Chapter 1 revealed that digital interventions are also efficacious for children and adolescents with depression and anxiety with moderate to large effect sizes when compared to non-active controls. This chapter further showed that the effect sizes of these interventions are typically smaller for younger participants, especially in the anxiety disorders and similar to the trend of falling effect sizes of conventional psychotherapy in younger age groups (Cuijpers et al., 2020; Zhou et al., 2019). Additionally, Chapter 1 outlined important research gaps, for example in regard to non-inferiority trials with established active comparators that are fundamentally lacking in children and adolescents, with the overall number of primary studies evaluating the effectiveness of digital interventions in youth being still limited and preliminary. Furthermore, in Chapter 2 it was found that digital interventions are effective in reducing panic and agoraphobia symptom severity in adults with a validated diagnosis of panic disorder and/or agoraphobia, with substantial effect sizes when compared to waitlist controls. Since IMIs were also meta-analytically evaluated to be similar effective as established active treatment conditions, these novel interventions can be conceived as a viable treatment alternative − not only for adults with subthreshold symptomatology, but also in patients with clinically relevant symptoms of diagnosed panic disorder with or without agoraphobia (Chapter 2). The findings of Chapter 1 and 2 are in line with newly formed meta-analytic evidence (e.g., Garrido et al., 2019; Pauley et al., 2021) and support the notion that digital interventions have an important role to play in extending mental health care services for patients with CMD across the lifespan.

In contrast, the systematic review and meta-analysis described in Chapter 3 pointed to a limited potential and restricted efficacy of digital interventions for the specific patient group of youth with chronic medical conditions. Here, only the meta-analytical evaluations on health-related self-efficacy and combined disease-related outcomes were significant, whereas the other meta-analyses on depression, quality of life and further secondary outcomes revealed non-significant findings, suggesting a limited benefit of digital interventions in this specific patient group (Chapter 3); a conclusion that is in line with the results of the review of Thabrew et al. (2018). Additionally, Chapter 4 revealed significant shortcomings in the quality of mobile-based interventions for CMD in youth, for example in regard to information quality and perceived impact of the apps, suggesting to temper the hype of digital

interventions especially for children and adolescents. This disenchantment seems even more justified, given the broad absence of systematic evaluations of the efficacy of mobile health apps for CMD in youth (Chapter 4), which can be also observed, yet to a lesser extent, in mobile-based interventions for CMD in adults (e.g., Sander, Schorndanner, et al., 2020; Sucala et al., 2017; Terhorst et al., 2018).

Taken together, the results of Chapters 1-4 document the general efficacy of internet-based interventions for CMD in different age groups, but also point to important limitations, especially in regard to the lack of efficacy studies on mobile-based interventions, and the restricted efficacy in interventions for younger patients and youth with chronic medical conditions. Notwithstanding, the established efficacy of digital interventions for several indications can be seen as a starting point for subsequent research on the active ingredients and change processes of these interventions, informing intervention development and scientific efforts towards improved interventions with larger effect sizes.

Conceptual considerations on digitalized psychotherapy process research

The field of psychotherapy process research has long suffered from the dispute of proponents of the common factors and specific factors models about the relative importance of common and specific factors (Mulder et al., 2017), and most importantly, from inconsistent operationalizations and imprecise applications of key research concepts (Cuijpers, Reijnders, & Huibers, 2019). These restraints have led to the current state "that little is known about the mechanisms of change of these therapies" (Cuijpers, Reijnders, & Huibers, 2019, p. 2), with a broad uncertainty *whereby* and *how* conventional psychotherapies for CMD actually work. In order to contribute to circumvent these shortcomings for the rather novel field of process research on digital mental health interventions, Chapter 5 introduced and outlined an integrative model of the active ingredients and mechanisms of change in digital interventions for depression. The purpose of this conceptual model (that can be also extended to other CMD) was to clearly define essential constructs, denote hypotheses on potential relationships between elements and to provide a paradigmatic framework for studies on change processes (i.e., component and mediation studies). Building on these conceptual considerations and definitions of key constructs, Chapter 6 discussed the novel opportunities but also the potential pitfalls that digitalized research approaches might bring for psychotherapy process research. Here, it was illustrated that central advantages of digital interventions for psychotherapy process research are in the possibilities 1) to facilitate direct experimental

manipulations of specific mechanisms that represent paradigmatic fragments of the complex processes of psychotherapies, 2) to detect high-resolution data on change processes within or outside therapy sessions, 3) to achieve larger sample sizes with resultant higher statistical power, 4) to control for confounding variables of face-to-face psychotherapies (e.g., therapist factors), and 5) to enable a higher standardization of intervention components, facilitating a more reliable detection of the effects of single components in dismantling design studies. The subsequent chapters on component and mediational studies exploited some of these assets, but were at the same time confronted with some of the challenges of digital mental health as outlined in Chapter 6, like high attrition rates and limited engagement in digital interventions (Baumel et al., 2019; Linardon & Fuller-Tyszkiewicz, 2020; Yardley et al., 2016).

Intervention components, and specific and common factors of digital interventions

It is well-established, that digital interventions with some type and amount of guidance are more effective than complete self-help interventions (Baumeister et al., 2014; Moshe et al., 2021). This advantage in efficacy is assumed to be primarily due to the adherence-facilitating function of guidance and the supportive accountability to a therapist or an "e-coach" (Domhardt & Baumeister, 2021; Mohr et al., 2011). Still, empirically-supported knowledge on other intervention components, representing specific and common factors of digital interventions, is scarce. A recent network-meta-analysis (Furukawa et al., 2021) found initial evidence that behavioral activation and "non-specific treatment effects components" contribute to incremental gains in the efficacy of internet-based Cognitive Behavioral Therapy (iCBT) for depression, and that the relaxation component had unfavorable effects on the reduction of depression symptom severity. Additionally, the intervention component behavior therapy for insomnia was evaluated to be helpful, yet based only on four component studies with weak evidence (Furukawa et al., 2021).

In Chapter 7 the available component studies on digital interventions for anxiety disorders were systematically reviewed and meta-analytically synthesized. The findings of this meta-analysis corroborated the superiority of guided over unguided interventions for anxiety, and further suggested that the qualification of e-coaches does not influence outcomes; a preliminary and controversial finding that is also in line with reviews on other CMD (Baumeister et al., 2014; Moshe et al., 2021; Titov, 2011). Furthermore, the meta-analytical

comparisons in Chapter 7 propose that interventions based on different theoretical foundations are similarly efficacious as CBT-oriented interventions in reducing anxiety symptoms, and that transdiagnostic approaches are as efficacious as disorder-specific interventions. However, given the limited number of primary studies in these comparisons, as well as the common limitation of restricted statistical power in component studies (Cuijpers, Cristea, et al., 2019), these findings have to be interpreted with caution and considered as preliminary, necessitating further high-quality non-inferiority trials with a priori defined non-inferiority margins. Overall, since IMIs for anxiety disorders achieved a large effect size when compared to digital attentional control groups, we can conclude that digital interventions do not work solely due to common (digital) factors or a "digital placebo effect" alone (Torous & Firth, 2016), but are reliant on several yet to be determined distinct specific factors in component studies with sufficient statistical power to detect small to very small effects. Nonetheless, these active ingredients of digital interventions do not completely tell us, what processes within patients are induced by these components and which mediators transmit the interventions effects. These issues are addressed with mediational studies that can be regarded as the essence and core approach of psychotherapy process research.

Mediators and mechanisms of change in digital interventions

In order to identify and evaluate the mediators and mechanisms of change in digital interventions, my co-authors and I have conducted four different studies (Chapters 8-11), and proposed and tested (Chapter 10) novel opportunities for the meta-analytical synthesis of the results of these mediation studies. In Chapter 8, we described a secondary analysis of a multicenter RCT on the effectiveness of a digital intervention to prevent depression-onset in patients with chronic back pain. This mediational study of 295 patients found that the interventions` effects on depression symptom severity were transmitted by quality of life (QoL), and, in more specific, by the QoL-subscales "coping" and "mental health", underscoring the particular significance of active coping as a mediator in digital interventions (Bakker et al., 2018) and psychotherapies for CMD in general (Groth et al., 2019; Lemmens et al., 2016). In this paper, we also discussed the importance to look at the specific operationalizations of potential intervening variables at the item- and subscale-level, in order to distinguish between actual and genuine change processes (i.e., the coping subscale) on the one side, and mediators that merely share a tautological and redundant overlap with the outcome symptomatology (i.e., the mental health subscale) on the other side (Chapter 8).

Two systematic reviews contribute to this part of the thesis, by comprehensively evaluating the available studies on the mediators and mechanisms of change in digital interventions for CMD in youth (Chapter 9) and for depression in adults (Chapter 11). Both reviews found a broad range of investigated mediators, with a particular prominence of cognitive variables (such as perceived control, rumination or interpretation bias), mirroring the findings of research on the mechanisms of change in face-to-face psychotherapies to a large extent (Lemmens et al., 2016; Ng et al., 2020). By highlighting methodological shortcomings of the included mediational studies, this thesis additionally intended to guide forthcoming mediation studies and contribute to findings with larger causal certainty in the future (Chapters 9 and 11).

Above and beyond the systematic review of mediational studies in digital interventions for anxiety disorders, Chapter 10 meta-analytically evaluated eligible mediators by using a novel two-stage-structural-equation-modelling approach. This statistical method for the synthesis of aggregated data of mediational studies revealed a significant indirect effect for negative thinking and non-significant indirect effects for combined cognitive variables, both in clinical and non-clinical samples; yet, these meta-analytical evaluations were limited by a very small number of studies. Furthermore, the largest group of examined mediators across studies were cognitive variables, evincing also the second highest proportion of significance; followed in numbers by skills and a wide range of other, affective and behavioral mediators, paralleling the findings of Chapters 9 and 11. For a detailed and in depth discussion of the findings of each single chapter, the reader is referred to the discussion section of each respective chapter.

Implications for research, intervention development and clinical practice

The findings of this thesis bring several implications for research, intervention development and clinical practice. To start, Part I of this thesis suggests that several digital interventions for CMD across age groups are effective, and can complement and extend current mental healthcare practices, given their special features like delivery independent from space and time, potential anonymity and cost-effectiveness. As such, the findings lend further support for the potential and relevance of digital interventions to contribute to improve global mental healthcare (Andersson et al., 2019; Torous et al., 2021).

Yet, this part of the dissertation revealed also significant shortcomings in digital mental health interventions, particularly the smaller effect sizes for younger participants, the non-significant

findings of digital interventions for youth with chronic medical conditions and the broad uncertainties about the evaluation of the efficacy of mobile-based interventions. These findings clearly indicate to balance the hope around digital interventions (Baumeister et al., 2021), and to carefully look at the actual potential of these interventions for different patient and age groups in routine care. Furthermore, given the limited efficacy of some digital interventions, further research is obviously needed that identifies pathways to improve interventions and contribute to increase the effect sizes of interventions. Part II and III highlighted some conceptual considerations and methodological recommendations for this kind of process research.

The knowledge on the active ingredients and mechanisms of change provided by this thesis can offer some insights for the empirically-informed advancement of interventions. For instance, the evidence of Part IV on the active ingredients of digital interventions for anxiety disorders have several implications for intervention development and clinical practice. First, in view of the advantages in efficacy of guided interventions compared to unguided interventions – a widely consistent finding across studies –, interventions should integrate some type and a minimum amount of guidance, in order to increase effect sizes (Chapter 7). Yet, on the other side completely self-guided interventions may offer a bigger potential for scaling-up evidence-based interventions for CMD since they can be completely technologically delivered (e.g., Karyotaki et al., 2017). Thereby, self-help interventions may have also an important role to play in the advancement of global mental health, notwithstanding their smaller effect sizes. Hence, both guided and unguided interventions have their warranted application and can contribute to alleviate the disease burden of CMD with their specific properties. Second, although the qualification of e-coaches might not be associated with the outcome, we recommend e-coaching provided by health care professionals, because guidance in real-world settings might not be as controlled as in research studies and there is insufficient knowledge on adverse events in relation to varying qualification levels so far (Chapter 7). Yet, potential risk and not benefit should be the primary outcome when it comes to scaling down qualification levels in healthcare systems (Baumeister, 2017). Third, interventions can be based on divergent evidence-based therapeutic orientations for anxiety, and transdiagnostic protocols may further enlarge the scalability of interventions to increase the number of patients that can be reached by one digital intervention (e.g., Weisel et al., 2019). Still, the numbers of primary studies in the meta-analytical comparisons in Chapter 7 were rather small and the implications based on these findings need to be confirmed by additional research.

The findings on the mediators and mechanisms of change in digital interventions for CMD across the lifespan bring several implications for intervention development and clinical practice (Chapters 8-11). First, Chapter 8 suggests that digital interventions for the prevention of depression in adults with chronic back pain should resort to intervention components supporting the active coping of patients. Essential components inducing the active coping of patients may be psychoeducation, behavioral activation, and training of problem solving skills as implemented in the CBT-based intervention that was evaluated here (Sander, Paganini, et al., 2020). Second, all three systematic reviews on the mediators of digital interventions pointed to a particular importance of cognitive mediators in the treatment of depression (Chapter 11) and anxiety in adults (Chapter 10), as well as for digital mental health interventions for CMD in youth (Chapter 9). Therefore, it appears that cognitive factors like rumination, negative thinking, perceived control, mastery, self-efficacy, or interpretation bias have an important role in transmitting the interventions effectiveness and it should be ensured that digital interventions for CMD stimulate and deploy these significant mediators. Third, further well-established mediators that current and newly developed digital interventions in clinical practice should exploit are acceptance and mindfulness, behavioral activation, emotion regulation (particularly in youth) and the usage of skills (Chapters 9-11).

The systematic evaluation of the risk of bias in primary studies, and most notably the rating of the methodological quality of process research have revealed several implications for the methodological advancement of future mediation studies. First, since there were considerable shortcomings of primary studies concerning the establishment of temporality and the experimental manipulation of mediators, upcoming studies should aim to attend to these central criteria of process research, in order to pave the way to detect causal relationships between interventions, mediators and outcomes (Chapters 9-11). Furthermore, it goes without saying that all other quality criteria for process research (i.e., study design with RCT and suitable control group; theoretical foundation of mediators; sample size $n \geq 40$ per group; testing of multiple mediators; significant relation between intervention, mediators and outcomes; dose-response relationship; specificity; Chapters 8-11) are important design features for informative mediation studies in the future. Digital interventions may also represent a new paradigm that contributes to overcome some of the persistent impediments of conventional psychotherapy research conducted face-to-face and facilitate the fulfillment of these quality criteria. Especially, digital interventions are highly standardized (dose-response relationship), provide the opportunity to deliver modular intervention components (experimental manipulation and specificity) and enable high-resolution data related to the

timing (temporal precedence), dose (dose-response relationship) and proximal outcomes (association) of intervention components and mediators. Furthermore, digital interventions can be scaled far more efficiently to attain the large sample sizes required to identify the (small to very small) effects of single active ingredients and mediators of therapeutic change. Second, these new process studies should aim to resort to more advanced approaches to statistical mediation analysis, like dynamic structural equation modelling (Grimm & Ram, 2018; Iacobucci et al., 2007), time lagged mediation analysis (Cole & Maxwell, 2003), latent growth curve modelling (Cheong et al., 2003; Soest & Hagtvet, 2011), causal mediation analysis (Imai et al., 2010; Mayer et al., 2014), or dynamic network approaches (Hofmann et al., 2020), circumventing the limitations inherent to the "causal steps" approach (Baron & Kenny, 1986), and capable to model the temporal ordering, as well as the actual shape of change (Chapters 10 & 11). Third, with Chapter 10 and a recently published paper (Domhardt et al., 2022) this thesis has defined novel approaches for the evidence synthesis of mediational studies that can be deployed by future meta-analyses on the aggregated and individual participant data level. As such, the accomplishments of this thesis go beyond the field of digital mental health, and bring also clinical and methodological implications for psychotherapy research and other process studies overall.

Strengths and limitations

This thesis possesses several strengths, and is characterized by its comprehensive scope as well as its high methodological rigor. The mechanisms of change in digital interventions were investigated in different CMD, in different age groups across the lifespan and for interventions with various evidence-based therapeutic approaches. Hereby, a wide array of methodologies and article types were employed (i.e., theoretical and perspective papers; umbrella review; systematic reviews; systematic evaluation of apps; randomized controlled trial; meta-analyses on efficacy, component and mediation studies). Furthermore, the papers adhered to the respective reporting guidelines (e.g., PRISMA for systematic reviews and meta-analysis; CONSORT for the RCT) and methodological standards of good scientific practice for each study type (e.g., use of standardized rating scales and validated instruments; risk of bias assessment; quality rating of criteria for process research; rigorous study selection and data extraction in reviews; pre-registration of the majority of studies). Moreover, the systematic reviews and meta-analyses included only RCTs, comprehensively covering the

respective research field, yielding the highest evidence and outlining important future directions.

Despite the strengths of this thesis, there are also limitations that should be considered when interpreting the findings. First, some reviews and meta-analytical comparisons were limited by a small number of primary studies. Accordingly, the implications based on the findings of some reviews must be reflected cautiously, and have to be considered as preliminary in some instances. The limited number of studies also circumvented some pre-planned subgroup and moderator analyses. Second, the focus on statistical significance and English language papers may have led to some degree of publication bias, although trial registries were searched for unpublished data within most reviews to counterbalance this bias. Third, some meta-analyses were confronted with a rather high clinical and statistical heterogeneity, which could not constantly be clarified or accounted for. Fourth, the generalizability of the findings in some systematic reviews and meta-analyses were reduced, since the majority of primary studies were conducted in western countries and represented samples with predominantly female participants. Fifth, some systematic reviews and the secondary analysis of the RCT were not pre-registered and were exploratory in nature. Sixth, there were methodological limitations in several primary studies themselves (e.g., small sample sizes; limited quality for process research and potential high risk of bias). Seventh, the majority of mediation studies used self-report instruments to assess depression outcomes and mediators alike, but masked clinician-rated interviews are considered to be the gold standard in outcome assessment. Finally, as an innate impediment of all mediation studies (Cuijpers et al., 2019; Kazdin, 2007), it cannot be ruled out that the mediation effects evaluated by this thesis might have been actually due to other unknown or unassessed proxy variables.

Future research

Personalization of interventions

Next to the evidence-based advancement of interventions itself, another important approach to improve treatment outcomes and to maximize the impact of interventions for a given individual is the personalization of treatment. The concept of "precision medicine" (or "personalized medicine") is broadly defined as "prevention and treatment strategies that take individual variability into account" (Collins & Varmus, 2015, p. 793). Precision medicine has the ultimate goal to secure the best match between the individual patient and the treatment, by

selecting an intervention (among the available options) before the initiation of treatment for a given individual that has the highest likelihood for a positive outcome (Cohen & DeRubeis, 2018; Cuijpers et al., 2016). A range of variables and corresponding algorithms are thought to inform and facilitate these evidence-based pretreatment selections, specific and tailored for a given individual. In the last decade, the personalization of treatment has received ever growing interest and is thought to impact virtually all fields of medicine and health sciences in the future (Collins & Varmus, 2015; Hamburg & Collins, 2010).

In the specific context of psychotherapy (research), the personalization of treatment has a long history (Cuijpers et al., 2016), and may be rooted back to Freudian times. The seminal sentence of Paul (1967) "What treatment, by whom, is most effective for this individual with that specific problem, under which set of circumstances?" – later extended by Paul (1969) with the process-relevant adjunct: "…, and how does it come about?" (p. 44) – has guided psychotherapy research for decades. Yet, the achievements of these research efforts were rather limited so far, and the recent opportunities associated with digitalization, big data and digital phenotyping (Montag & Baumeister, 2023) may depict a turning point for the personalization of psychotherapeutic interventions (Domhardt et al., 2021). Indeed, recent examples in psychotherapy research (DeRubeis et al., 2014) and digital mental health (Furukawa et al., 2021; Karyotaki et al., 2021) underscore this trend and further nourish hopes for the future benefits related to the personalization of interventions.

Process-based approaches

Traditional psychotherapy (process) research and clinical psychological science as a whole may have reached a tipping point, since their conventional conceptions, guiding principles and research approaches are to be criticized for several reasons (Hofmann & Hayes, 2019). First, in the last decades a strong focus was laid on the development and evaluation of syndrome-specific treatment protocols, although the latent disease entities that are the foundation and target of these protocols are not proven and of doubtful validity (Hayes et al., 2020). While this approach certainly has its merits and has led to great achievements in mental health, the central goals of conceptual and treatment utility are not achieved by these protocols (Hayes et al., 2020). Second, the dominance of disorder-specific protocols has also brought along the tendency to overlook the idiosyncratic characteristics of individual patients and to neglect the relevance of specific situations and contexts for salutary processes and patients' well-being. A tendency which was also amplified by the dominant nomothetic

research approach of RCTs, applying the findings that are based on groups and averages to the individual patient, largely disregarding differences between individual patients. Third, the mechanisms of change in psychotherapies were long studied by mediational studies within the framework proposed by Baron & Kenny (1986). Yet, this approach is incapable to adequately grasp the processes of change in psychotherapeutic interventions, "because it falsely assumes that treatment change is a linear, unidirectional, pauci-variate process and that the statistical assumptions are met to study processes of change in an individual using a nomothetic approach" (Hofmann et al., 2020, p. 1). As such, the "causal steps" approach suggested by Baron and Kenny is too simplistic and not suited to capture the complexities and dynamics of change processes in psychotherapeutic interventions. For some scholars, including the author of this thesis, the innovations of process-based therapy may offer solutions to the aforementioned impediments of clinical psychology, and may represent a major paradigm shift that transforms clinical intervention science and has the potential to improve treatment outcomes for individual patients.

Process-based therapy (PBT) is thought to be neither a new therapy nor another eclectic approach. It is thought to represent a model of models, and is intended to assist clinical assessment, conceptualization, and treatment (Hofmann & Hayes, 2019). It is best understood as a new framework and general approach to organize evidence-based therapeutic techniques along basic psychological dimensions relevant to human adaptation to a given context. Here, the psychological dimensions are represented and organized in an "Extended Evolutionary Meta-Model" (EEMM; Hayes et al., 2022), and include cognition, attention, affect, behavior, self, and motivation, as well as bio-physiological and sociocultural levels. Furthermore, PBT is embedded in an evolutionary background and applies the principles of variation, selection, retention and context to human adaptation and behavior change.

PBT stresses the importance to focus on the individual patient in each particular context. It is thought to overcome the nosological restrictions of the biomedical model and the corresponding syndrome classifications of the ICD or DSM approaches. In contrast to the biomedical model, PBT rather "reflect(s) a conceptualization of psychopathology as networks of interrelated biopsychosocial processes and problems that form a causal and dynamic network in ways unique to each person. Thus, even if two people present to therapy with a similar complaint, their prescribed treatments may vary depending on the person's individual network of ways of addressing problems this is causing or maintaining this complaint" (Ong et al., 2022, p. 2). Therewith, PBT is neither nomothetic nor ergodic, and focuses on the idionomic analyses of change processes, resorting to a multidimensional and dynamic

network approach (Hofmann et al., 2020). The key feature of PBT in clinical practice is to combine and tailor evidence-based procedures/techniques that induce evidence-based processes appropriate to the particular problems of a given patient in a specific situation (Hofmann & Hayes, 2019). Thereby, PBT places much less focus on protocols for syndromes and more emphasis on evidence-based processes linked to evidence-based procedures, aiming to foster the prosperity of individual patients (Hofmann & Hayes, 2019).

Overall, along with the personalization of psychotherapeutic interventions, PBT may be another important path towards improved treatment outcomes in mental health. This new paradigm aims to better grasp the complexities of psychotherapy and corresponding analyses of processes, to accommodate the specifics and idiosyncrasies of individual patients and guide future research – with an even more pronounced importance of empirically-supported knowledge on the active ingredients and mechanisms of change, which are the core themes of this thesis. By extending and updating Paul's 1969 seminal declaration, the authors of PBT have proposed a guiding light for future (process) research in their overarching question: "What core biopsychosocial processes should be targeted with this client given this goal in this situation, and how can they most efficiently and effectively be changed?" (Hofmann & Hayes, 2019, p. 38).

Further future directions

The findings of this thesis highlight several additional research priorities for future studies in digital mental health. In regard to the efficacy and effectiveness of interventions a range of unresolved research questions should be pursued by future research. These are for example essential information concerning the long-term effects of interventions, precise knowledge on the effect sizes for younger children (<14 years), necessary head-to-head comparisons with established face-to-face psychotherapies and cost-effectiveness studies on digital interventions for youth. Furthermore, the systematic reviews identified further knowledge gaps in regard to the safety of digital interventions, particularly in children and adolescents, as well as profound uncertainties around the effectiveness of mobile-based interventions across age groups.

At this time, we are conducting a largescale multicenter RCT, evaluating the effectiveness of a digital intervention for youth with chronic medical conditions and comorbid depression or anxiety (Lunkenheimer et al., 2020). With this study we aim to contribute to close current

knowledge gaps by providing results on the long-term effects, cost-effectiveness, and safety of iCBT as well as on the potential mediators (e.g., behavioral activation, automatic thoughts, coping, self-efficacy, stress-related growth, social support and therapeutic alliance) of treatment effects in this pediatric population. This study will generate further evidence of high-methodological rigor on the actual potential of digital interventions for youth with chronic medical conditions, and may challenge or confirm the rather sobering findings of the meta-analysis described in Chapter 3.

Although emerging meta-analyses on digital interventions for CMD provide important initial knowledge on the relevance of distinct interventions components (Domhardt et al., 2019; Domhardt et al., 2020; Furukawa et al., 2021; Moshe et al., 2021), several specific research questions are unsettled to date. It is still not known, for instance, what the necessary amount of guidance is, which automated support functions are a viable alternative to human support and how deterioration and adverse events are best handled in completely unguided digital interventions. Furthermore, a central issue in digital mental health are the questions how to increase the engagement of patients and how to ensure adequate adherence rates, since "effective engagement" (Yardley et al., 2016) is a prerequisite for actual "therapeutic activities" in patients to evolve (Baumel, 2022). Likewise, future studies are needed to investigate the novel conceptualization of common and specific digital factors (Chapters 6, 10 and 11), and substantiate or falsify this new concept, which was originally developed in the context of this thesis. A recent factorial trial on the intervention components of a mobile-based intervention for subthreshold depression (Sakata et al., 2022) may be a paradigmatic example for this kind of high-quality research, informing us about the relevance and differential efficacy of distinct (digital) specific and common factors of digital interventions for CMD.

Based on the findings of all three systematic reviews on the mediators and mechanisms of change, important implications for future research are to close current knowledge gaps on the processes of digital interventions based on theoretical approaches other than CBT, on the processes that are associated with negative effects and deterioration rates, as well as to identify distinct mechanisms of change in certain subgroups (i.e., moderated mediation). These future studies can contribute to improve interventions that possess limited effect sizes so far (e.g., interventions for children and adolescents; mobile-based interventions), facilitate the personalization of treatment and inform the dissemination of digital mental health interventions into routine care.

Conclusions

This thesis investigated the active ingredients and mechanisms of change in digital interventions for common mental disorders across the lifespan, by using a range of different study types and methodologies. Overall, the findings provide important information for the evidence-based advancement of interventions, clinical practice and future research in digital mental health:

a) Digital interventions are effective for several CMD in different age groups. Hence, they can be an important means to improve global mental health, considering their specific features and advantages. This conclusion applies especially for internet-based interventions and interventions for adults, which possess the best empirical support so far.

b) However, this thesis revealed at the same time that digital interventions might not be effective for certain indications, and evince smaller effect sizes in children and adolescents. Moreover, the evidence base in regard to mobile-based interventions is insufficient, necessitating future research in regard to their respective efficacy and effectiveness.

c) Future studies can make use of the novel possibilities and advantages of digitalized research approaches for psychotherapy process research, and should adhere to central theoretical considerations and important definitions of key concepts. These studies should additionally identify pathways to further improve interventions and increase effect sizes, as well as amend persistent impediments of digital mental health, such as limited engagement and restricted adherence rates.

d) Intervention components that contribute to the efficacy of digital interventions are guidance and modules that support the active coping of patients. Meta-analytical evidence on other components suggest that the qualification of e-coaches, the respective therapeutic approach and the disorder-specificity of the intervention may not make a difference for efficacy in anxiety disorders. Yet, these findings have to be considered preliminary given the limited number of component studies on these issues.

e) A wide range of different mediators and mechanisms of change transmit the effects of digital interventions for CMD in different age groups, with a particular prominence of cognitive variables. Across studies, the best established significant mediators are reductions in dysfunctional cognitions, acceptance, mindfulness, self-efficacy, perceived control and mastery, as well as emotion regulation particularly in youth. Digital interventions should contain treatment components that induce these essential processes of change.

f) This thesis described and tested novel methodological ways for the evidence synthesis of mediation studies and the evaluation of mediators. Upcoming research may exploit these approaches to comprehensively evaluate the complex mechanisms of change in psychological interventions for the prevention and treatment of mental disorders in future meta-analytic studies.

To conclude, digital interventions possess the potential to improve global mental health. Yet, future research efforts are certainly needed, to increase the effect sizes for specific patient populations and treatment modalities, as well as to substantiate the implementation of digital interventions into routine care. This thesis may inform some of these scientific endeavors and may contribute to the evidence-based advancement of interventions for CMD across the lifespan.

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