Top-funded companies offering digital health interventions for the prevention and treatment of depression: a systematic market analysis

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Abstract

Background Digital innovations can reduce the global burden of depression by facilitating timely and scalable interventions. In recent years, the number of commercial Digital Health Interventions for Depression (DHIDs) has been on the rise. However, there is limited knowledge on their content and underpinning scientific evidence. This study aimed to: (i) identify the top-funded companies offering DHIDs and (ii) provide an overview of their interventions, including scientific evidence, psychotherapeutic approaches and use of novel technologies.

Methods A systematic search was conducted using two venture capital databases to identify the top-30 funded companies offering DHIDs. In addition, studies related to the DHIDs' were identified via academic databases and hand-searching. The methodological quality of the publications was evaluated using the Mixed Methods Appraisal Tool.

Results The top-30 funded companies offering DHIDs received a total funding of 2,592 million USD. Less than half of the companies produced any scientific research associated with their DHIDs, with a total of 83 publications identified. Twenty-five publications were randomised control trials, of which 15 reported moderate-to-large effects in reducing depression symptoms. Regarding novel technologies, few DHIDs incorporated the use of conversational agents or low-burden sensing technologies.

Conclusions Funding received by top-funded companies was not related to the amount of scientific evidence provided on their DHIDs. There was a strong variation in the quantity of evidence produced and an overall need for more rigorous effectiveness trials. Few DHIDs used automated approaches such as conversational agents, limiting their scalability.

Keywords Digital health interventions, Companies, Depression, Prevention, Treatment, Smartphone applications, Conversational agent, Just-in-time intervention, Low-burden sensing technologies

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Background

Depression is a common mental health disorder affecting over 300 million people worldwide [1, 2]. Studies indicate that the prevalence of depression has increased by nearly 50% over the last 30-year period [2], with a significant spike in depression cases during the COVID-19 pandemic [3]. Depression is responsible for a yearly economic burden of 210,5 billion USD in the US alone [4], driven by an increased risk of other comorbid mental and physical disorders, decreased functioning and quality of life, and early mortality [5]. Although effective treatments and therapies exist to help prevent depression and promote recovery [6], the majority of individuals suffering from depression remain untreated or receive minimal treatment in most countries [7].

Standard treatments for depression include psychotherapy and/or medication [8], which are administered by highly trained professionals. Due to the shortage of qualified mental health providers in many regions of the world, alternative treatment options are of great importance [9]. Individuals at risk or diagnosed with depression might benefit from accessible therapies that are easy to master and implement. Digital Health Interventions for Depression (DHIDs) are a scalable alternative to traditional, in-person treatments [10–12].

Evidence indicates that digital interventions are effective in treating behavioural and mental health problems across the lifespan [13–16]. Several controlled trials of DHIDs conducted over the past twenty years have shown moderate to large effects for the prevention and treatment of depression [10, 17–20]. However, there is considerable variation in their effectiveness [15, 18, 21–23], which might be explained due to DHIDs differing greatly in terms of their features, mode of delivery, and therapeutic approach. For example, some DHIDs are blended (i.e., websites and/or mobile applications which include access to a clinician or a coach as part of the treatment package),

while other DHIDs only feature self-guided components, without the need for a coach or clinician [24, 25].

DHIDs may also incorporate novel technologies, such as Just-in-Time Adaptive Interventions (JITAIs), which deliver an adaptive intervention at a time when the user is thought to be more vulnerable (i.e., prone to experiencing adverse health outcomes) and receptive (i.e., prone to receiving, processing, and utilising the support provided) [26–28]. Moreover, conversational agents are a rapidly growing approach to digital health in which users interact with computer programs that facilitate a human-like dialogue through auditory or textual methods, with the potential to improve uptake and engagement [29]. Similarly, low-burden sensing technologies [30] are able to capture real-time data which may include physical signs (e.g. facial expressions and activity) and physiological signs (e.g., heart rate variability and breathing), both of great interest in the mental health domain.

Over the last decade, the number of commercial digital health interventions on the Internet and on mobile phone marketplaces has increased [31]. In 2022 alone, venture capital companies invested a record figure of 700 million USD across 72 mental health companies [32]. The COVID-19 pandemic is thought to have acted as a catalyst for commercial DHIDs, as remote mental health services were suddenly required for an increased number of people [33], driving interest and uptake [34]. Despite the rising popularity of commercial DHIDs, little is known about their main features or whether they are evidence-based interventions. To address such gap in the literature, the present review aims to: (i) identify the top-funded companies offering DHIDs and (ii) provide an overview of their interventions, with a focus on the underpinning scientific publications, targeted population, psychotherapeutic approaches, regulatory approval, and use of novel automated approaches such as conversational agents, JITAIs or low-burden sensing technologies. In doing so, we aim to assist stakeholders (e.g., healthcare providers, administrators, policymakers, and potential patients) in critically evaluating the current landscape on commercial DHIDs and make informed choices based on the underpinning scientific evidence. In addition, findings might inform future DHIDs' development and evaluation efforts.

Methods

The Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) statement was followed for the conduct and reporting of this review. A completed PRISMA checklist is available as online Supplementary material 1.

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Search strategy

Companies. Digital mental health companies offering DHIDs were identified using two venture capital databases: Crunchbase and Pitchbook. Both databases are among the most comprehensive venture capital databases and are commonly used as data sources for academic reports and by investors [35], including previous market analyses in the field [36, 37]. Venture capital databases collect information and statistics related to companies relevant to a given industry, including details such as funding rounds, investment amounts received, and/or geographical locations of the companies. The search process was conducted in October 2020 (updated in May 2022) and included a list of terms describing the constructs "verticals, methods, and industries" and "depression and mental health" (Table 1).

Publications. Once the final list of companies was defined, PubMed, Cochrane library and PsycInfo were searched in October 2020 (updated in May 2022) to identify publications related to the companies' DHIDs. The search strategy included the following key words: "Name_Intervention" AND (Smartphone OR Application OR App OR Intervention OR Mobile Health). That is, for each included company (e.g., Lyra Health, Inc.) we searched for the name of its DHIDs (e.g., Lyra Health) and the above keywords (Smartphone OR Application, etc). In addition to the electronic search, the companies' websites and the reference list of included studies were hand-searched to identify additional publications.

Inclusion criteria

Companies. Digital mental health companies were defined as registered enterprises focused on the development and commercialisation of DHIDs. Informed by the World Health Organisation's definition of digital health interventions [38], we conceptualised DHIDs as interventions delivered remotely through a wide variety of approaches such as websites, smartphone apps, text message-based interventions, or conversational agents, as well as interventions that combine a mobile phone component with additional support. For example, mobile phone-based intervention used to augment a

Table 1 Search terms used in venture capital databases (PB = Pitchbook, CB = crunchbase)

Search category	Search terms
Verticals, Methods and Industries	PB: Digital Health* OR Information Technology* > Software > Application Software OR Mobile* OR Big Data OR Artificial Intelligence & Machine Learning* AND (*Include Related Keywords) CB: Health Care OR Apps OR Big Data OR Artificial Intelligence OR Mobile AND (Applying Full Description as additional filter criterion)
Depression and Mental Health	PB: Depression OR Mental Health CB: Depression OR Mental Health

clinician-delivered intervention [20]. We did not consider interventions that were delivered exclusively by mental health practitioners via videoconferencing or telephone (i.e., teletherapy). Companies that did not primarily address depression were also excluded, for example, those offering general wellness interventions targeting diet and exercise which make unsubstantiated claims to be able to improve mood and help with depression. In addition, companies where the end-user was not the "patient" (i.e., the individual who will receive intervention for depressive symptoms) were also excluded (e.g., apps targeted at healthcare providers for managing their caseload remotely). Lastly, we excluded companies that only offered peer support or forum platforms, as well as those that were not available in English.

It is worth noting that not all companies that met the inclusion criteria were included in the review. Considering one of our main aims was to evaluate the underpinning scientific evidence of the included DHIDs, we decided to focus on the top 30 companies as these are likely to be the ones that are better equipped (in terms of manpower, funding and experience) to conduct research and publish the results. This is the same approach used in previous systematic market analyses [37, 39]. A significant positive correlation exists between the amount of funding a company receives and the quantity and quality of research publications it produces [40]. Moreover, the included companies represent a sizeable portion of the total market, approximately 50% according to CB insights [41].

Publications. Eligible publications included studies testing potential effects of the DHIDs (e.g., randomised controlled trials, quasi-experimental studies), as well as studies analysing other relevant aspects of the intervention such as feasibility, adherence, engagement, user satisfaction, cost-effectiveness, and digital markers. This was done to account for a wider scope of research beyond intervention studies that can shed light not only on intervention effectiveness, but also on the contexts and mechanisms through which these effects are present [42–44]. Protocol studies, proof-of-concept studies, systematic reviews, and commentary papers were not included in the analysis as they do not report metrics that are reflective of the benefits that the end-user gains from the DHIDs.

Selection process

Companies. After removing duplicates between Crunchbase and Pitchbook, the remaining companies were reviewed by five independent researchers working in pairs to assess whether they met the inclusion criteria (OC, AS, AA, GWT, and KL). Any disagreement between reviewers was resolved by discussion. If required, disagreement was resolved through a consensus discussion

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with a third reviewer (AS). To validate the list of companies meeting the selection criteria, two external experts with extensive industry and academic experience in the field of mental health were invited to review the included companies and associated interventions. This was done to ensure that we did not miss major players within the field of DHIDs. Two additional companies were included as a result. Finally, companies were ranked according to funding, with the top-30 being included for extraction.

Publications. The selection of relevant publications followed the same procedure as with the companies' selection. Reviewers worked in pairs to independently screen the publications identified through database or manual searches from the top-30 companies and assess whether they met the inclusion criteria. This was done is two stages: title and abstract screening (1st stage) and full-text screening (2nd stage).

Data extraction
Companies. Data extracted for the top-30 companies included: (i) total funding, (ii) prevention and/or treatment of depression, (iii) target population, (iv) mode of delivery, (v) digital therapeutic approval by regulatory bodies (if applicable); (vi) psychological approach (e.g., Cognitive Behavioural Therapy), (vii) use of novel technologies (e.g., conversational agents), (viii) operating system (e.g., iOS), (ix) country, and (x) language(s) used. These data were extracted from a variety of sources, including the venture capital databases, the companies' websites, the identified publications, and the offered DHIDs, which were accessed by the research team when possible (e.g., by downloading the relevant app). If needed, the included companies were approached by the research team for further clarification regarding the data items extracted as well as to seek permission to access the DHIDs (if not available). This resulted in all included companies being contacted to sought clarification on one or more items extracted. In the case of conflicting funding information between the two databases, Crunchbase Pro data were reported due to better coverage of financing rounds and total capital committed [35].

Publications. Selected publications were categorised into three different groups to provide a high-level overview of the types of research conducted by mental health companies on their DHIDs. The first group (level I) included randomised controlled trials (RCTs), as they are recognised as the 'gold-standard' for studying intervention effectiveness [45], the second group (level II) included non-randomised, quasi experimental intervention studies, and the third group (level III) included a variety of research designs that are related to interventions but not necessarily address effectiveness (e.g., studies focused on feasibility, adherence, engagement, user satisfaction, cost-effectiveness, and digital markers). This classification was based on the US Preventive Services Task Force hierarchy of research designs, which is commonly used to assess the quality of evidence in a given field [46]. In addition, year of publication and reported effectiveness (for level I and II publications) were also extracted.

Appraisal of studies
The methodological quality of the included studies was evaluated using the Mixed Methods Appraisal Tool (MMAT). The MMAT is a valid and reliable tool that allows appraisal of five different categories of studies: qualitative research, RCTs, non-randomised studies, quantitative descriptive studies, and mixed methods studies [47]. Quality indicators depend on the specific study category and include, for example, the appropriateness of the study design, the choice of sampling strategy, the adherence to the methods for collecting data, the integrity of the intervention, or the integration of findings. Two reviewers (AS, AA) independently applied the tool's methodological quality indicators to each of the publications included in the review. Any disagreements on ratings were resolved through discussion between the two reviewers. An overall score ranging from 0 (lowest methodological quality) to 100 (highest methodological quality) was computed for each study according to the tool's pre-specified criteria. A complete overview of MMAT results is available as Supplementary material 2.

Data analysis
The information extracted from the companies, publications, and DHIDs was summarised narratively. Descriptive statistics were used to analyse the amount of funding and number of studies per company. Linear regression was used to investigate the relationship between the amount of funding received and the number of publications produced by each included company.

Results
Selection and inclusion of companies
The search yielded a total of 259 companies on Crunchbase Pro and 202 companies on Pitchbook. After removal of duplicates and screening against the selection criteria, a total of 77 companies were deemed eligible for inclusion. These companies were then reviewed by two mental health experts, who suggested the inclusion of two additional companies not identified through the database search. The companies were later sorted in terms of funding and the top-30 funded companies were included in the review. The top-30 funded companies accounted for 97.6% of the total funding in all the 79 companies that met our selection criteria. Figure 1 outlines the selection process and reasons for exclusions.
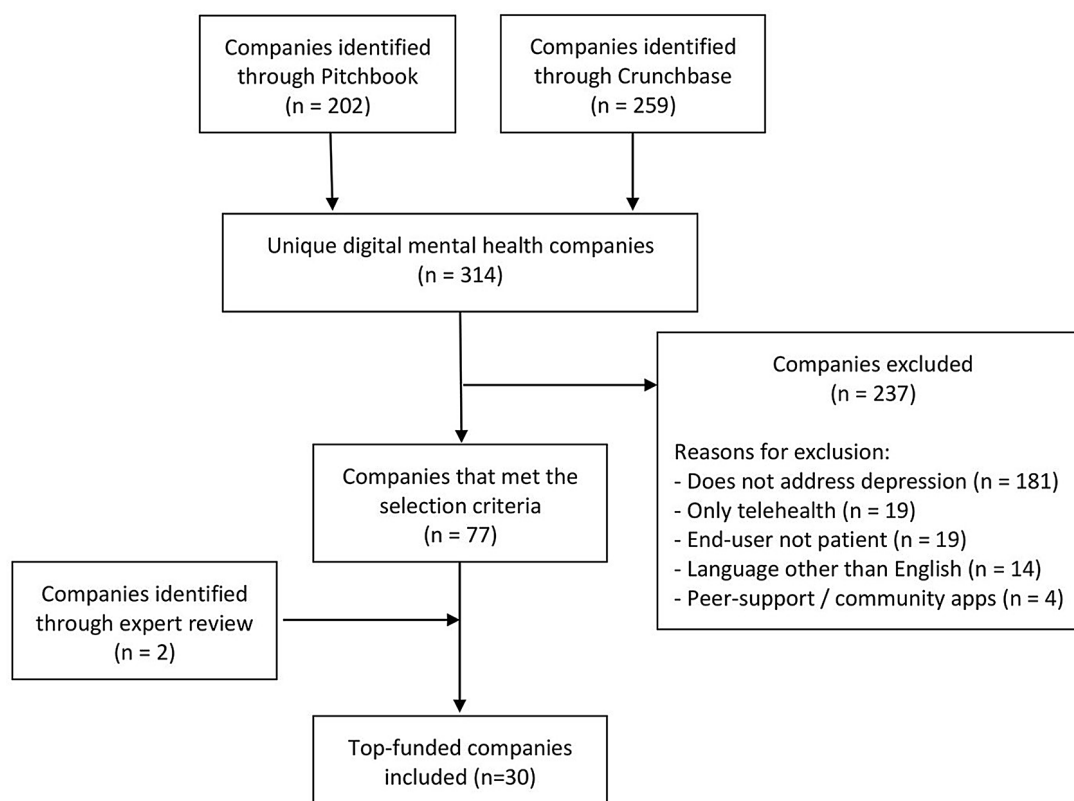
Fig. 1 Flow diagram of the companies' selection process

Characteristics of the included companies

Table 2 contains an overview of the funding amount received by the companies and the scientific evidence provided for the included DHIDs. The funding amount of the 30 DHIDs companies ranged from 13 to 910 million USD (mean=106; median=59), with the top-funded company (Lyra Health) accounting for almost one-third of the total funding (910 million out of 2,592 million USD). Most companies were based in the US (n=22/30, 73.3%), followed by the UK (n=2/30, 6%), Sweden (n=2, 6%), India (n=2/30, 6%), Spain (n=1, 3%), and Germany (n=1/30, 3%). The majority of companies offered DHIDs exclusively in English (n=20/30, 66.6%), with only one third (n=10, 33.3%) available in other languages (i.e., Spanish, Swedish, German, French, Portuguese, Italian, Greek, and Chinese).

The DHIDs targeted different groups, including employees (e.g., DHIDs as part of an Employee Assistance Programme; n=17/30, 56.6%), clients of health insurance programmes (n=12/30, 40%), general adult population (n=11, 36.6%), and adolescents (n=1/30, 3%). Access to the DHIDs varied according to the target population. Interventions that were freely available (n=7/30, 23.33%) tended to focus on general adult population, while DHIDs with limited access (e.g., via access code only; n=23/30, 76.6%) tended to be part of an employee

assistance or health insurance program. Some of the DHIDs which were freely available contained 'premium' features that could only be accessed upon paying a subscription fee (n=4/30, 13.3%).

Most of the DHIDs identified followed a blended approach (n=25/30, 83.3%), combining tele-health (e.g., video or text-based chat) with self-guided components (e.g., mobile app and/or website including breathing tools or use of journaling). The rest focused exclusively on stand-alone components, with no human interaction (n=5/30; 16.6%). These self-guided DHIDs tended to be the ones directed at the general population.

In terms of the psychological approach underpinning the DHIDs, Cognitive Behavioural Therapy (CBT) was frequently reported in the majority of companies (n=26/30, 86.6%) followed by mindfulness (n=19/30, 63.3%), in which only a few DHIDs (n=6/30, 20%) specified their scientific foundation (e.g., Mindfulness-Based CBT or Mindfulness-Based on Stress Reduction). Other psychotherapeutic approaches reported were evidence-based interventions focusing specifically on depression (n=8/30; 26.6%), such as Behavioural Activation (BA) and/or Interpersonal therapy (IPT). Dialectical Behaviour Therapy (DBT), which is typically used as part of crisis interventions or severe emotional regulation problems, was cited in some DHIDs (n=7/30, 23.3%). Additionally,

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Table 2 Overview of the included companies and their digital health interventions for depression

DHID	Provider	Funding (Million USD)	Target population	Psychological Intervention	Services provided	Other novel technologies (e.g., CAs, EMA, Sensing)	Operating System	Country & language(s)	Total No of publications
Lyra Health	Lyra Health, Inc.	910	EAP, Employees	CBT, ACT, DBT, ET, UP, Mindfulness	- Face-to-face support - Remote support (Video therapy, txt-based, phone (crisis intervention)) - Self-guided components	---	Not an app (website)	U.S. (English)	3
Ginger	Ginger.io, Inc	220	EAP, Employees	CBT, Mindfulness	- Remote support (Video therapy, txt-based) - Self-guided components	EMA, Mood tracker	Android, iOS	U.S. (English)	3
Quartet	Quartet Health Inc	219	Health insurance, health providers	CBT	- Face-to-face - Remote support (Video therapy, Online-platform)	---	iOS	U.S. (English)	0
Vida Health	Vida Life Inc	188	EAP, Employees	CBT, Mindfulness	- Remote support (Video therapy, txt-based) - Self-guided components	---	Android, iOS	U.S. (English)	2
Modern Health	Modern Health, Inc.	167	EAP, Employees	CBT	- Remote support (Video therapy, txt-based, live-community) - Self-guided components	---	Android, iOS	U.S. (English)	0
Mind strong	Mindstrong Health	159	EAP, health insurance, health providers	CBT, Crisis management	- Remote support (Video therapy, phone, txt-based, measurements in the mobile app)	Digital biomarkers	Android, iOS	U.S. (English)	0
Happify	Happify, Inc.	118	General population	CBT, PP, ACT, DBT, PST, IPT, BA, ET, MBSR, crisis intervention	- Self-guided components - Gamification - Online-community	Biofeedback HRV, breathing. Conversational Agent	Android, iOS	U.S. (English, French, Chinese, Japanese, Spanish, German, Portuguese, Italian)	6
Woebot*	Woebot Health	113	General population	CBT, DBT, IPT, Mindfulness	- Self-guided components	EMA, Mood tracker. Conversational Agent	Android, iOS	U.S. (English)	2
Deprexis	Orexo	73	Health insurance, clinical population	CBT, BA, IPT, SFT, MBCT, relaxation, Physical activity and lifestyle modification (exercise and nutrition), SFC, PP, Dreamwork and EFT	- Remote support (Video) - Self-guided components	---	Not an app (website)	Sweden (English, German, Greek, French, Italian, European Portuguese, and Swedish)	16
Unmind	Unmind Ltd.	63	EAP, Employees	CBT, PP, ACT, MBCT	- Remote support (helplines and local healthcare providers) - Self-guided components	EMA, Mood tracker. Conversational Agent	Android, iOS	UK (English)	1

Table 2 (continued)

DHID	Provider	Funding (Million USD)	Target population	Psychological Intervention	Services provided	Other novel technologies (e.g., CAs, EMA, Sensing)	Operating System	Country & language(s)	Total No of publications
Meru Health	Meru Health	51	EAP, Employees, health providers, Health insurance	CBT, BA, MBCT, MBSR, Holistic intervention (sleep, nutrition, habits)	- Remote support (phone, chat-based coach support, virtual workshops) - Online-community	Biofeedback and HRV with a wearable device	Android, iOS	U.S. (English)	9
Koa Health/Mindset	Koa Health B.V	44	Healthcare, Health insurance, EAP	CBT, PP, Mindfulness	- Remote support (Video therapy, txt-based) - Self-guided components	–	iOS, website	Spain (English)	0
NeuroFlow	NeuroFlow, Inc.	31	Government, military population, health providers	CBT, DBT, ET, Mindfulness	- Remote support (Video therapy) - Self-guided components	Track behaviours (sleep, activity, mood, stress and pain)	Android, iOS	U.S. (English)	3
Brightside Health	Brightside Health Inc.	31	(EAP) Employees, health providers	CBT	- Remote support (Video therapy, txt-based)	–	Not an app, Website	U.S. (English)	0
Limbix	Limbix Health Inc.	31	Adolescents (13–22 years old)	Psychoeducation, CBT, BA, PST, Mindfulness	- Remote support (Video therapy) - Self-guided components	EMA, Mood tracker, Conversational Agent	Android, iOS	US English	0
Spring Health	Spring Care, Inc.	29	EAP	CBT, Mindfulness, Holistic intervention (exercise, diet, sleep)	- Remote support (Video therapy) - Face-to-face support - Self-guided components	EMA, Mood tracker	Android, iOS	U.S. English	0
Valera Health	Valera Health	26	General population, clients of insurance companies and health providers	CBT, Mindfulness, Psychoanalysis	- Remote support (Video therapy) - Self-guided components	-	Android, iOS	U.S. English, (Spanish, simplified Chinese)	1
Space from depression/Anxiety	Silver Cloud Health	26	EAP, clients of insurance companies and health providers	CBT, BA, PP, ET, Mindfulness	- Remote support (txt-based) - Self-guided components	EMA, Mood tracker	Android, iOS and website	U.S. English Spanish German	17
Learn to Live	Learn to Live, Inc.	15	EAP, insurance companies and health providers, students	CBT	- Remote support (Video therapy, phone, txt-based). - Self-guided components	-	Not an app (website)	U.S. English	0
Mindler	Mindler AB	13	General population	CBT	- Remote support (Video therapy, txt-based chat) - Self-guided components	-	Android, iOS	Sweden Swedish / English	0

Table 2 (continued)

DHID	Provider	Funding (Million USD)	Target population	Psychological Intervention	Services provided	Other novel technologies (e.g., CAs, EMA, Sensing)	Operating System	Country & language(s)	Total No of publications
Wysa*	Wysa Ltd.	9.3	General population, EAP	CBT, DBT, Mindfulness	- Remote support (Txt-based chat) - Self-guided components	Conversational Agent	Android, iOS	India (English, Hindi, Punjabi & Bengali)	2
Kintsugi Hello	Kintsugi Mindful Wellness, Inc.	9.0	General population	CBT, DBT	- Self-guided components - Community support	Voice biomarker for detection	iOS	US English, Spanish	0
HelloBetter	Geton-institut.de	9.0	General population, clients of certain insurance companies	CBT, BA, PST, healthy sleeping, physical activity	- Remote support (Video therapy) - Self-guided components	EMA, Mood tracker	Android, iOS -Website	Germany English, German	13
Shine*	Shine, Inc.	8.2	General population, EAP.	ACT, Mindfulness	- Self-guided components -Community support (monthly virtual workshops)	EMA, Mood tracker (only in the premium version). Conversational Agent	Android, iOS	U.S. English	0
My Online Therapy	Lekta Therapy Ltd.	6.0	General population	CBT, ACT, DBT, IPT, CAT, Couple therapy, EMD, MBCT,	- Remote support (Video therapy) - Self-guided components	Conversational Agent	Website+app Android, iOS	UK English	0
myStrength	myStrength, Inc.	5.8	people under certain EAP and health providers	CBT, PP, ACT, Mindfulness	- Remote support (Video therapy) - Self-guided components	-	Android, iOS	US English	4
InnerHour	InnerHour	5.6	General population, EAP.	CBT, PP, Mindfulness, ACT, physical activity	- Remote support (Video therapy) - Self-guided components	EMA (mood tracker). Conversational Agent	Android, iOS	India English	0
wayForward	PsyInnovations Inc	4.7	General population, EAP, and health providers	CBT, PP, DBT, Mindfulness	- Remote support (text-based, phone) - Self-guided components	-	Android, iOS	US English	0
Mindoula	Mindoula Health, Inc.	4.2	Comorbid conditions and clinical population, health providers	CBT	- Face-to-face support - Remote support (Video therapy, phone) - Self-guided components	EMA (mood tracker)	Android, iOS	US English, Spanish	0

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Table 2 (continued)

DHID	Provider	Funding (Million USD)	Target population	Psychological Intervention	Services provided	Other novel technologies (e.g., CAs, EMA, Sensing)	Operating System	Country & language(s)	Total No of publications
Youper AI Therapy	Youper, Inc.	3.5	Students, general population, health insure companies	CBT, ACT, DBT, PST, MBCT	- Remote support (Video therapy) - Self-guided components	Conversational agent	Android, iOS	U.S English	0
Total		2,592							83

*Indicates the intervention is freely available

DHID: Digital Health Intervention for Depression; **CAs:** Conversational agents; **EMA:** Ecologic Momentary Assessment; **HRV:** Heart Rate Variability; **EAP:** Employee Assistance Program; **CBT:** Cognitive Behavioral Therapy; **BA:** Behavioral activation; **ACT:** Acceptance and Commitment Therapy; **DBT:** Dialectical Behavior Therapy; **IPT:** Interpersonal Therapy; **ET:** Exposure Therapy; **UP:** Unified protocol; **PP:** Positive Psychology; **PST:** Problem Solving Therapy; **SFC:** Schema-Focused Content; **EFI:** Emotion Focused Interventions; **CAT:** Cognitive Analytic Therapy; **MBCT:** Mindfulness-based cognitive therapy; **MBSR:** Mindfulness-Based Stress Reduction

Positive Psychology (PP) ($n=8/30$, 26.6%), Problem Solving Therapy (PST) ($n=4$; 13.3%), and Acceptance Commitment Therapy (ACT) ($n=7$, 23.3%) were also cited. Apart from the psychotherapeutic approaches mentioned, some DHIDs ($n=4/30$, 13.3%) also included intervention components related to healthy lifestyle, such as physical activity, nutrition and/or sleep.

Regarding approval by national regulatory bodies, only 3 DHIDs were found to be approved as digital prescription interventions. These were developed by: (a) Orexo –approved by the Food and Drug Administration (FDA) in the US; (b) HelloBetter – approved by the Federal Institute for Drugs and Medical Devices (BfArM) in Germany; and (c) SilverCloud Health – approved by the National Institute for Care Excellence (NICE) in the UK. Four additional companies (16%) had a pre-certification by the FDA: Happify (prevention of depression & anxiety), Woebot (postpartum depression), NeuroFlow (depression in teenagers), and Wysa (depression & anxiety). These companies obtained pre-certification as part of the emergency approval during the COVID-19 pandemic.

Regarding novel technologies, only a few companies incorporated the use of conversational agent ($n=8/30$, 26.6%) in their DHIDs. Ten companies (33.3%) implemented JITAI components in the form of Ecological Momentary Assessment for mood-tracking. In relation to sensing technology, some companies used breathing biofeedback (HRV) ($n=3/30$, 10%), or involved tracking sleep, stress, mood, and/or pain through a wearable device ($n=3/30$, 10%). Only one DHID incorporated the use of voice biomarkers for the detection of depression and anxiety.

Scientific evidence on commercial DHIDs

A total of 83 publications were identified (Fig. 2). The publications' date ranged from 2009 to 2022, with the majority of them (56 out of 83, 67.4%,) published during 2017 and 2022. Over half of the companies ($n=16/83$, 53.3%) did not seem to produce any scientific output and a big proportion of publications ($n=46/83$, 56.7%) were published by only three companies (SilverCloud Health, Orexo, and HelloBetter). Out of the 83 identified publications, 25 (30%) were classified in level I (i.e., RCTs), 25 (30%) in level II (i.e., quasi-experimental studies), and 33 (42.1%) in level III (i.e., studies not related to the DHIDs' effectiveness but to other aspects such as feasibility, user satisfaction, engagement, or cost-effectiveness). The number of publications did not correlate with the total amount of funding ($r2=0.01$) (See Figure in Supplementary material 3).

In terms of RCTs (level I), Orexo/Deprexis had the highest number of trial ($n=12/25$, 48%), followed by HelloBetter ($n=5/25$, 20%) and SilverCloud ($n=3/25$, 12.0%).
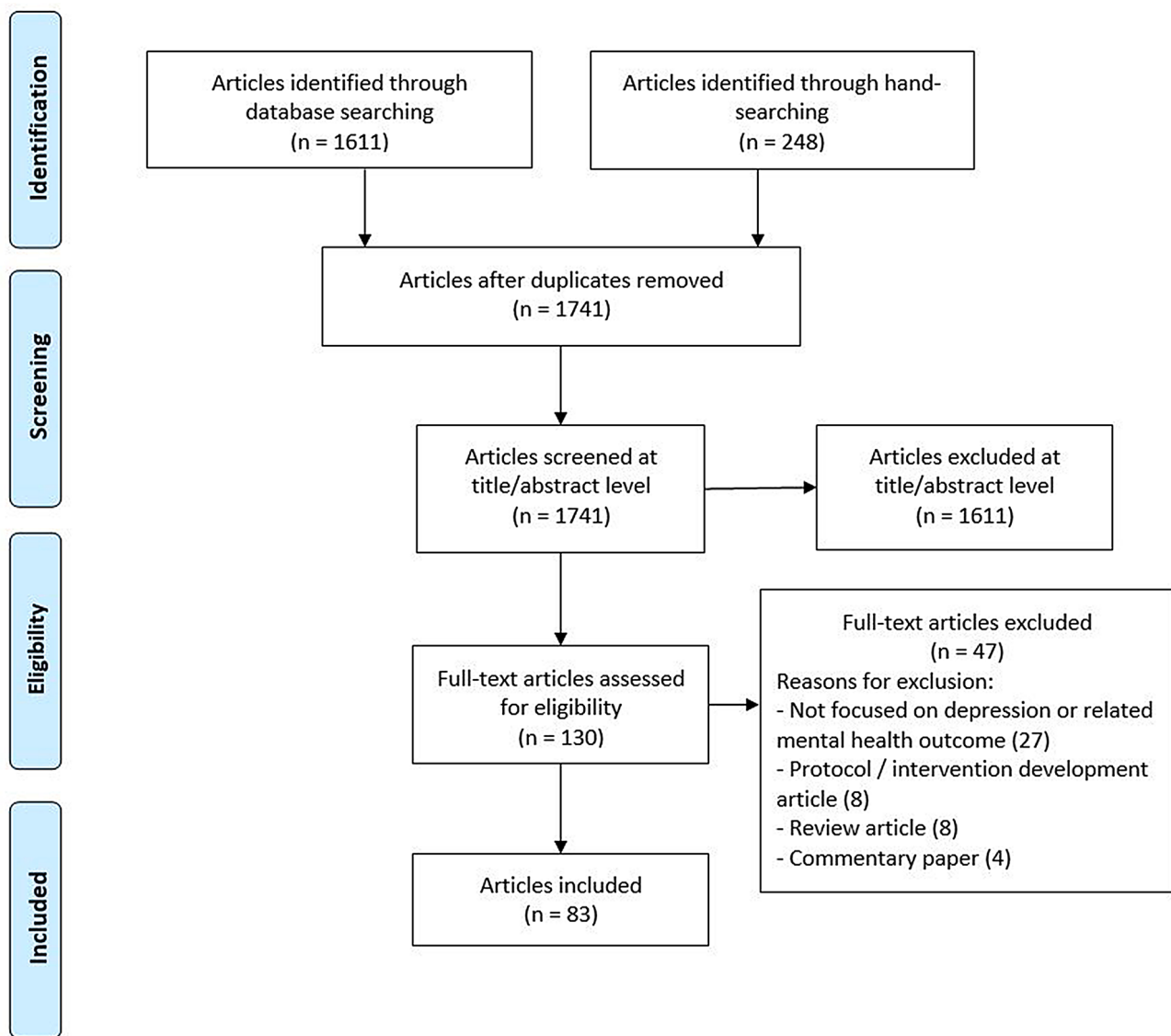
Fig. 2 Flow diagram for the articles included in the systematic market analysis of digital mental health interventions for the prevention and treatment of depression

Out of 25 RCTs, 16 (60%) reported moderate-to-large effect sizes between groups with depressive participants in website interventions [48–62]. There were two RCTs (8%) that reported small effect sizes and were conducted with subthreshold depression participants [63, 64]. Seven (28%) RCTs found no significant differences between groups [65–71].

Among level II (quasi-experimental studies), Silver-Cloud ($n=8/25$) and Meru health ($n=5/25$) had the greatest number of studies. In 23 out of the 25 studies, statistically significant differences were found within group of individuals with depression [72–75], including HRV app [76], indirect depression (insomnia) [77], and severe depression [78]. No significant differences were reported in three studies [$n=2/25$; 8%], including a study

with physicians [79], and indirect depression prevention (resilience) [80].

Within level III, a variety of studies were conducted by a total of 12 companies (40%), among which only three companies (Deprexis, HelloBetter, and myStregth) conducted cost-effectiveness evaluation studies of their DHIDs. The cost-effectiveness studies demonstrated that digital interventions for depression [81], and depression symptoms in diabetic adults [82, 83] reduced health care costs.

Results of the MMAT quality assessment
Out of the 83 included publications, 25 (30%) were categorised as RCTs; 42 (49%) as non-randomised studies, including quasi experimental intervention studies and

observational studies (e.g., cohort or cross-sectional), eight as mixed-method studies (9.6%), five as qualitative studies (6%), and three as quantitative descriptive studies (3.6%), including incidence or prevalence studies without comparison group.

For RCTs, overall scores ranged from 20 to 100 (mean=68; median=60). In three out of 25 RCTs, the randomisation was not clearly performed [56, 67, 69] and sixteen out of the 25 RCTs did not report participants' adherence to the assigned interventions [49–52, 54, 56, 57, 59, 64–66, 70, 71, 84]. For the reminder, adherence was conceptualised using different compliance metrics with the intervention, such as satisfaction, working alliance, subjective qualitative feedback, frequency and/or time spent in the intervention [48, 53, 55, 60, 63, 67, 69, 82]. For non-randomised studies, scores ranged from 20 to 100 (mean=62.3; median=60). All five qualitative studies scored 100. These studies analysed the experience of the users with the intervention, including focus group discussions [85, 86], interviews [87, 88], and barriers/facilitators regarding blended interventions with therapists [89]. For mixed-methods studies, scores ranged from 40 to 100 (mean=90; median=100). Last, for quantitative descriptive studies, scores ranged from 60 to 100 (mean=80; median=80). A complete overview of the quality assessment, including reviewers' ratings for each methodological quality criterion, is available as an Additional file 2.

Discussion

To the best of our knowledge, this review is the first to identify the top-funded mental health companies focused on the prevention and/or treatment of depression and to provide a comprehensive overview of their DHIDs and underpinning research. We summarise below the main review results and make recommendations for future DHID's development and evaluation in light of the findings.

Commercial DHIDs

Only a small number of DHIDs (*n*=4/30, 13.3%) included intervention components targeting physical activity, nutrition and/or sleep. That is, the majority of DHIDs were not holistic interventions but rather focused solely on depression. This conflicts with contemporary views on mental health, which emphasise the care of both mind and body and highlight the significance of the whole human entity and the interdependence of its parts, including body, mind, connectedness, and spirituality [90]. Qualitative studies with potential users have also shown a generally positive attitude towards holistic health [91, 92] and thus it is likely that future commercial or research-based DHIDs will benefit from incorporating a range of lifestyle components.

With regards to the psychological approaches used, the majority of DHIDs were based on CBT (*n*=25, 83.3%), which is the approach that has been proven most effective in the treatment of depression [8]. However, the details regarding the specific CBT ingredients implemented were missing in the majority of DHIDs, except for the companies with more scientific evidence (i.e., SilverCloud, Deprexis, and HelloBetter), which clearly specified the active components used for the treatment and prevention of depression (e.g., behavioural activation). The poor reporting in relation to key CBT features raises the question as to whether these DHIDs are truly implementing a CBT approach, which may negatively impact their efficacy for depression [93, 94]. Current and future mental health companies will benefit from clearly defining their psychological approach, as opposed to loosely referring to CBT as the main driver of the intervention.

Many of the DHIDs used a blended approach, relying on human assistance to deliver the intervention (*n*=26, 86.6%). This means only a few of the DHIDs included in this review are scalable interventions that could be implemented at the population-level. Meta-analyses have demonstrated that fully automated interventions are potentially effective for depression [95], which leaves opportunities to increase scalability and access to treatment by leveraging on novel technologies (e.g., conversational agents, JITAIs). In this regard, the majority of the DHIDs in this review did not incorporate any novel technology, with only eight (26.6%) of them making use of conversational agents. Recently, the novel ChatGPT and other generative AI conversational agents have been released to the public and are being increasingly used for a wide range of applications. Specific to DHIDs, AI conversational agents present promising features such as emotion detection and sentiment analysis capabilities to better understand conversations with users and respond accordingly [96]. However, there are still concerns regarding safety, privacy and anonymity that will need to be addressed before widespread adoption in the healthcare domain [97].

Regarding the implementation of JITAI in the DHIDs, most of them used a related approach called Ecological Momentary Assessment (EMA), which was implemented specifically for mood-tracking. EMA was incorporated into the DHIDs of 10 companies (33.3%). Additionally, some companies (*n*=5/30, 16.6%) mentioned digital biomarkers of mental health symptoms or tracking behaviours (sleep activity, stress, pain), as well as biofeedback breathing. Nevertheless, it was not clear how these technologies were implemented. Using sensing data explicitly linked with depression was also limited to a single company that owns a biomarker voice (Kintsugi). According to a recent review, the development of both research and commercial DHIDs is still lagging behind in technology

integration and development [28]. For the field of digital therapeutics to progress to the next level, it will require a more innovative approach as well as studies investigating how to best integrate novel technologies within existing DHIDs.

Last, in terms of target population it is worth noting that only one of the DHIDs focused on adolescents. The reminder DHIDs targeted adults, especially employees (n=17, 56.6%). DHIDs are a potentially useful approach to reach and offer support to adolescents, as they are native digital consumers [98] in which depression and other mental health disorders are frequently reported [99]. Therefore, DHIDs developed with public research funds might need to prioritise this population subgroup, which is somewhat neglected by top-funded commercial DHIDs. Interventions tailored to meet the needs of children and teens offer the opportunity to support and prevent depression throughout the lifespan.

Scientific evidence on commercial DHIDs

Approximately half of the top-funded companies produced research, and this was unrelated to the amount of funding received (i.e., companies with higher funding did not produce a higher number of publications). This suggests other factors might be more relevant to explain why some companies conduct research while others do not. One of such factors is likely to be the presence of researchers in the company. For example, SilverCloud Health was co-founded by an adjunct professor and HelloBetter started as a research project at the Leuphana University of Lüneburg. These two companies, together with Orexo, produced the majority of studies included in this review (46/83, 56.7%).

In the rapidly developing DHIDs' industry, return on investment needs to be shown quickly, whereas in academia the methodological approaches and measures that are used to test intervention effectiveness are more time-intensive [100–104]. This could explain why half of the included companies did not produce any scientific output. However, mental health companies might invest more in research in the future as there is a growing emphasis on developing evidence-based interventions [105]. A recent case study of five companies providing digital health solutions showed that 3 out of the 5 companies reported feeling more motivated to work with research collaborators as it encouraged a strong psychological evidence base to their interventions than when developers did not have an academic background [101]. Research-tested products may also improve regulatory appeals and have a competitive edge from being able to make scientific claims [105]. For example, the DHIDs from the three companies with most scientific publications (i.e., SilverCloud Health, HelloBetter and Orexo)

were the only ones approved as digital therapeutics by national regulatory bodies.

Besides the number of studies that companies conducted to investigate their DHIDs, the nature of these studies is also worth considering. From the 83 studies identified, 30% were RCTs (level I), 30% of studies investigated effectiveness through quasi-experimental trials (level II), and the reminder 40% of studies investigated other aspects such as feasibility, engagement, and digital markers (level III). In terms of RCTs, and similar to the total number of studies, SilverCloud Health, Deprexis and HelloBetter had the highest number of trials. This means that the majority of commercial DHIDs from top-funded companies have not been formally evaluated by means of an RCT, or at least results have not been published as peer-reviewed scientific publications. RCTs remain the gold standard for evidence, allowing for the DHID's effects to be studied while controlling for other potentially confounding variables, and are often necessary for an intervention to be recognised by national regulatory boards and be reimbursed by insurers [106, 107]. It is worth mentioning that more than half of the included RCTs (15/25, 60%) showed moderate-to-large effects in reducing depression symptoms, which highlights the potential of DHIDs implementation into the health care system.

DHIDs hold a great potential for the prevention of depression as they provide a scalable, low-cost, first line of support tool. Based on the information contained on the website or in reported studies, we classified most of the included companies as aimed at both prevention and treatment of depression. However, very few studies in this review targeted prevention explicitly. Future research investigating DHIDs should focus on prevention as it can be more effective and less expensive than the treatment of diseases.

There was also an absence of innovative experimental trials (e.g., factorial, SMART, micro-randomised trials) that provide direct information about the effectiveness of individual intervention components (and/or different variations of them). The Multiphase Optimization Strategy (MOST) framework [108], a leading approach for digital health intervention development, poses that devoting time and effort to optimising the intervention via experimental trials is a critical and often overlooked step prior to conducting a formal evaluation through an RCT. While RCTs are helpful to investigate the effectiveness of the intervention as a package, they are not designed to provide nuanced information on the effectiveness of individual components, which would allow further optimisation [107].

Strengths and limitations

A strength of this study is that two researchers independently carried out the different stages of the review process (screening, data extraction, quality assessment), reducing the risk of errors and maximising reliability. In addition, all included companies were approached to ensure accurate data extraction and the search strategy included two different venture capital databases and validation of selected publications by mental health experts.

Some limitations must also be acknowledged. Our review focused on a specific subset of companies (top-30 in terms of funding) and thus results might not be applicable to all DHIDs currently available in the market. Similarly, since our results indicate that funding is not correlated to scientific output, we could have missed relevant publications from companies that do not meet the top-30 funded threshold but are prolific in terms of scientific production. In addition, despite our comprehensive search efforts, including two popular venture capital databases and a review of the combined search results by two mental health experts, it is possible that some relevant companies were missed (e.g., if not included within the two selected databases or indexed using terms other than 'depression' or 'mental health'). Last, another potential limitation of our findings is an increased risk of bias in the included studies due to selective reporting by the companies, which might be incentivised to suppress negative or undesirable findings of their products. The scientific process (i.e., pre-registration of trials, peer-reviewed publications, being transparent about potential conflicts of interest) might have helped mitigate these risks to some extent.

Conclusions

The top-30 funded companies offering DHIDs received a total funding of 2,592 million USD up to May 2022. According to our results, the total number of publications produced was unrelated to the funding received by companies. In addition, the amount of evidence on the different DHIDs varied considerably, with a few companies conducting most of the research. The majority of commercial DHIDs from top-funded companies have not been rigorously evaluated, or results have not been made available through peer-reviewed scientific publications, and thus little is known about their effectiveness (or lack of). While companies often reported evidence-based psychotherapy and mindfulness approaches, details on the specific therapeutic ingredients were limited. Most DHIDs relied on human support; few interventions used automated approaches such as conversational agents, JITAIs or low-burden sensing technologies, resulting in limited scalability and reach.

Abbreviations

DHIDs	Digital Health Interventions for Depression
JITAIs	Just-in-Time Adaptive Interventions
RCTs	Randomised Controlled Trials
MMAT	Mixed Methods Appraisal Tool
CBT	Cognitive Behavioural Therapy
BA	Behavioural Activation
IPT	InterPersonal Therapy
DBT	Dialectical Behaviour Therapy
PP	Positive Psychology
PST	Problem Solving Therapy
ACT	Acceptance Commitment Therapy
FDA	Food and Drug Administration
BfArM	Federal Institute for Drugs and Medical Devices
NICE	National Institute for Care Excellence
EMA	Ecological Momentary Assessment
MOST	Multiphase Optimization STrategy

Supplementary Information

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> Supplementary Material 1
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> Supplementary Material 2
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> Supplementary Material 3

Author contributions

OC, AS, AA, and TK conceptualised the study and manuscript. OC, AS, and AA designed and implemented the search strategy. OC, AS, AA, GWT, and KL screened and extracted data from the apps, websites, and studies. OC, AS, and AA analysed the data and drafted the initial manuscript with feedback by TK. All the authors reviewed and edited the final manuscript.

Data availability

No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate
Not applicable.

Consent for publication
Not applicable.

Competing interests

OC, GWT, EF and TK are affiliated with the Centre for Digital Health Interventions, a joint initiative of the Department of Management, Technology, and Economics at ETH Zurich and the Institute of Technology Management at the University of St. Gallen, which is funded in part by the Swiss health

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