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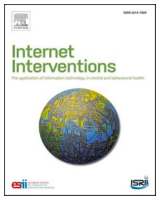

A systematic review of predictors and moderators of treatment outcomes in internet- and mobile-based interventions for depression

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ABSTRACT

This systematic review aimed to synthesize evidence on predictors and moderators of treatment outcomes in internet- and mobile-based interventions (IMIs) for depression, informing personalized care. A systematic search across PubMed, PsycInfo, and Cochrane yielded 33,002 results. Two reviewers independently performed screening, data extraction, risk of bias assessment, and methodological quality evaluation. Fifty-eight single studies (m = 466 analyses) focusing on baseline-predictors (59.7 %, m = 278), process-predictors (16.5 %, m = 77), and moderators (21.9 %, m = 102), and six individual patient data meta-analyses (m = 93) were included. Only 24.0 % (m = 112/466) of analyses in single studies and 15.1 % (m = 14/93) in individual patient data meta-analyses were significant. Evidence from single studies was rated as insufficient for all variable categories with only 2 out of 40 categories showing >50 % significant results. Baseline depression severity had the strongest predictive value with higher scores linked to better outcomes followed by variables indicative for the course-of-change. Other frequently analyzed and potentially relevant variables with significant results were adherence, age, educational level, ethnicity, relationship status, treatment history, and behavioral variables. More high quality quantitative studies with sufficient power are essential to validate and expand findings, identifying predictors and moderators specifically relevant in IMIs to explain differential treatment effects.

1. Introduction

Depression is a highly prevalent mental disorder (Wittchen et al., 2011; World Health Organization, 2017, 2022) associated with substantial impairment and a reduced quality of life in affected individuals (Saarni et al., 2007; Üstün et al., 2004; Whiteford et al., 2013). Internet- and mobile-based psychological interventions (IMIs) are recommended for depression treatment (Bundesärztekammer (BÄK) et al., 2022; National Institute for Health and Care Excellence, 2022) due to their medium to large effect sizes (Königbauer et al., 2017; Moshe et al., 2021) and comparable efficacy to that of face-to-face psychotherapy (Carlbring et al., 2018; Cuijpers et al., 2019).

However, similar to face-to-face therapy (Lambert, 2004, 2017), not all patients treated with IMIs benefit to the same extent, with some benefitting to a great extent and others not responding to treatment or even experiencing symptom deterioration (Cuijpers et al., 2021; Ebert et al., 2016; Karyotaki et al., 2018b; Rozental et al., 2019). A solution to optimize individual outcomes of IMIs for depression is to identify and explain differential treatment responses and personalize interventions by assigning and tailoring them according to patients' needs (Insel, 2009; Simon and Perlis, 2010).

Studying predictors and moderators of treatment outcomes can provide valuable insights into differential treatment responses. To be considered predictors or moderators, variables must precede treatment outcomes in time and be associated with them (Kraemer et al., 2008). A moderator is a factor that precedes treatment, is unrelated to the

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treatment itself, and influences the treatment's effect on the outcome, which means there is an interaction between the moderator and the treatment (Kraemer et al., 2002, 2008). A predictor, on the contrary, has a main effect on the outcome across or in single treatment groups and may turn out to be a moderator, mediator, or non-specific predictor in further research. Predictors occurring before the start of an intervention (i.e., baseline variables) can be indicative of a potential moderation effect, whereas predictors occurring in the course of treatment may emerge as mediators in further investigations (Kraemer et al., 2002).

In face-to-face therapy, findings on predictors or moderators such as age, comorbidity, social support, or symptom severity are often inconsistent, indicating a need for further research on these potentially relevant variables (Cuijpers et al., 2016; Kautzky et al., 2019; Kessler et al., 2017; Tanguay-Sela et al., 2022). Predictors and moderators of treatment outcomes in IMIs for depression have been investigated in single studies as well as aggregated across studies via individual patient data (IPD) meta-analyses. Compared to single studies that analyze data solely from their specific sample populations, IPD meta-analyses aggregate and reanalyze the primary data from multiple independent studies. Yet, a comprehensive overview of the overall evidence on predictors and moderators in IMIs for depression is lacking. IPD meta-analyses provide an evidence base with well-powered analyses of predictors/moderators with data from multiple studies (Cuijpers et al., 2022). However, selection bias hinders the acquisition and analysis of all pertinent data, such as instances where the authors of eligible articles cannot be reached (Andersson et al., 2019). Moreover, only variables standardly collected across studies can be analyzed.

Thus, the aim of our systematic review was to provide a comprehensive overview of the current evidence on predictors and moderators of treatment outcomes of IMIs for depression to inform further research on personalized mental health care in IMIs for depression. For that reason, we synthesized results of predictor and moderator analyses of both single studies and IPD meta-analyses on different treatment outcomes (symptom severity, improvement, response, remission, and deterioration).

2. Methods

This systematic review was preregistered at the Open Science Framework (OSF) Registries (https://osf.io/t9rsg). The first preregistration of this review (https://osf.io/5asc4) was withdrawn due to changes in our search strategy and eligibility criteria, which were made between the first preregistration and the start of the systematic searches. Reporting is based on the PRISMA statement (Moher et al., 2009).

2.1. Eligibility criteria and search strategy

In this systematic review, we included single trials on treatment outcome predictors/moderators investigating (a) an IMI (b) targeting depression with (c) depression as the primary outcome. Blended interventions and telemedicine or treatments in which the internet was used only for communication or which were equivalent to face-to-face therapy but were conducted via telephone, video, or text-based communication between a patient and a therapist were excluded. The types of studies included depended on whether moderators or predictors were investigated: for studies examining predictors, (d_1) a pre–post study design with one single treatment group was sufficient for inclusion; studies investigating moderators had to be (d_2) randomized controlled trials (RCTs) or secondary analyses based on RCTs with an active or non-active control condition.

The participants had to be (e) adults (≥18 years of age) and had to have (f) a diagnosis of a depressive disorder or elevated symptoms of depression, as assessed by applying a commonly used clinical cutoff score on a validated measure. We included studies that (g) statistically analyzed at least one variable that had been assessed before the post-treatment outcome assessment as a predictor or moderator of the treatment outcome. Any statistical methods (e.g., including simple correlation) were considered. In addition, relevant IPD meta-analyses were identified from a systematic review of IPD meta-analyses of psychological treatments targeting depression (Cuijpers et al., 2022).

The following outcomes were considered: (a) symptom severity defined as post-treatment depression severity, (b) improvement defined as the change in depression symptoms from pre- to post-treatment, (c) treatment response defined as the application of a predefined criterion of clinically significant improvement (percentage improvement or improvement of the primary outcome measure based on a specific cutoff score), and (d) remission, defined as the absence of clinically relevant symptoms at post-treatment (no diagnosis of depression at post-treatment or remission according to a specific cutoff score on the primary outcome measure). Because of the expected small number of trials addressing symptom deterioration, moderators and predictors of (e) any indicator of the worsening of symptoms were included.

Systematic searches were conducted on December 11, 2020. An update of the search was performed on November 21, 2022. The three electronic databases PubMed, Cochrane, and PsycInfo were searched using search terms indicative of "depression" or "anxiety" and "IMI" and "predictor" or "moderator." Search terms indicative of anxiety were included, as the search string was also used for another review of moderators and predictors of IMIs targeting anxiety (https://osf.io/kd5yh), for which the screening was carried out in parallel. The full search strategy is available in Appendix A. After removing duplicates, the titles and abstracts of the identified studies were screened. In a second step, the full texts of potentially eligible studies were reviewed for inclusion by two researchers (T.S. & M.S.) independently. Differences in the ratings of eligibility of these two reviewers were resolved by discussion or by consulting a third reviewer (A.Z. & D.E.). Additional relevant studies were identified by searching the reference lists of the eligible articles and studies included in recent review articles of IMIs targeting depression.

2.2. Data extraction and synthesis

The following data were extracted: (a) bibliographical data (authors, year, title, and country), (b) study design features (target disorder, control group, sample size, outcomes, times of assessment, and inclusion/exclusion criteria), (c) sample characteristics (diagnostic criteria, age, and gender), (d) intervention characteristics (name, content, guidance, treatment duration, and study adherence), and (e) predictors/moderators (measures, statistical methods, analyzed variables, significant variables (rounded p-value < 0.05), and direction of the association with the outcome (positive association, defined as higher scores of a continuous variable or a specified category of a categorical variable associated with a better treatment outcome; negative association, defined as higher scores of a dimensional variable or a specified category of a categorical variable associated with a worse treatment outcome; no information, defined as a lack of information on the direction of the association between a variable and the treatment outcome)). Definition criteria of our classification of predictors and moderators was based on Kraemer et al. (2002, 2008). If any of the required data were not provided, the authors were contacted, or, for eligible studies on secondary analyses, the initial publication of the trial was searched for missing information. Two researchers (T.S. & M.S.) performed the data extraction using a previously created template.

A descriptive approach for data synthesis was used. The identified variables were categorized as moderators (i.e., variables preceding intervention and interaction with treatment tested), baseline-predictors (i.e., variables preceding intervention and no interaction tested), process-predictors (i.e., variables occurring after intervention start and no interaction tested), and other (i.e., information on definition criteria missing or not meeting definition criteria) and then classified into main thematic categories and subcategories. Significant and nonsignificant results and the direction of the association between the variables and

outcomes were reported for each category.

2.3. Assessment of the risk of bias and methodological quality

The quality of the included single studies was rated by two independent reviewers (T.S. & M.S.) using two complementary assessment approaches on: (a) the general risk of bias (RoB) and (b) the methodological quality of assessing moderators and predictors based on the criteria by Pincus et al. (2011).

We used the revised Cochrane risk-of-bias tool for randomized trials (RoB 2; Sterne et al., 2019) for RCTs and the Risk Of Bias In Non-randomized Studies - of Interventions tool (ROBINS-I; Sterne et al., 2016) for non-RCTs. The RoB 2 tool was used to assess (a) randomization process, (b) deviations from the intended interventions, (c) missing outcome data, (d) measurement of the outcome, and (e) selection of the reported result, resulting in an overall judgment of a low RoB, a high RoB, or some concerns (Sterne et al., 2019). The ROBINS-I tool for non-RCTs was used to assess biases (a) due to confounding, (b) in the selection of participants into the study, (c) in classification of interventions, (d) due to deviations from intended interventions, (e) due to missing data, (f) in the measurement of outcomes, and (g) in the selection of the reported results, resulting in a low, moderate, serious, or critical RoB, or no information (Sterne et al., 2016).

To assess the methodological quality of the predictor and moderator analyses, we examined: (a) mention of a specific a priori statement about the intention of testing predictors/moderators, (b) evidence- or theory-based selection of predictors/moderators, (c) measurement of predictors/moderators prior to randomization (not applicable (NA) for studies that analyzed process-predictors), (d) adequate quality of the measurements of predictors/moderators as indicated by the availability of published evidence on quality criteria, and (e) specific testing of interaction presented (NA for studies that analyzed predictors; Pincus et al., 2011). The criteria were rated as yes/no questions and, in total, were classified as providing confirmatory evidence (all criteria fulfilled or NA), exploratory evidence (criterion 4 fulfilled and criterion 3 and 5 fulfilled or NA), or insufficient evidence (any other case).

2.4. Combined quality and global status of evidence

To be able to assess the global status of evidence of the extracted predictors/moderators by considering both the RoB rating and the methodological quality rating, an adaptation of the Best Evidence Synthesis Rating System for systematic reviews in this field was used (Conejo-Cerón et al., 2020; Moreno-Peral et al., 2020a; Moreno-Peral et al., 2020b). In the first step, a combined quality rating per study was calculated. The combined study quality was rated as good if a study displayed an overall low RoB (RoB 2/ROBINS-I) and provided confirmatory evidence regarding the methodological quality of the predictor and moderator analyses. The combined quality was rated as unsatisfactory when a study was classified as providing insufficient evidence or when its overall RoB was high (RoB 2) or serious or critical (ROBINS-I) and was classified as providing exploratory evidence. The remaining combinations of the RoB rating and the methodological quality rating were rated as satisfactory.

In the second step, the classification of the global status of evidence was performed at the level of variable categories of predictors/moderators. For a predictor/moderator category to be classified as strong, ≥75 % of the analyses had to be statistically significant in three or more studies, and the combined quality of these studies had to be predominantly good. A classification of moderate evidence meant that ≥65 % of the analyses within a category was statistically significant in ≥2 studies and that the combined quality of these studies was predominantly satisfactory. Finally, the evidence for a category was classified as insufficient if the proportion of significant analyses within the category and/or combined quality of the studies was not sufficient to fulfill the criteria for strong or moderate evidence.

3. Results

3.1. Study selection

In total, 33,002 articles (first search: 21,692, second search: 11,310) were identified through systematic searches of the PubMed, PsycInfo, and Cochrane electronic databases. Five additional records were identified by searching the reference lists of eligible studies. After the removal of duplicates, titles and abstracts of 23,088 records (first search: 15,994, second search: 7094) were screened for eligibility. Of these records, 651 articles (first search: 516, second search: 135) remained for full-text screening. In total, we included 58 articles (first search: 48, second search: 10) from 43 trials (see Appendix B for a list of all included articles). Detailed information about the study flow and reasons for exclusion are provided in Fig. 1. The full-text screening inter-rater reliability resulted in a Cohen's kappa of 0.68, indicating moderate agreement (McHugh, 2012).

3.2. Characteristics of single studies

Table C.1 in Appendix C displays an overview of the characteristics of the included articles. Twenty-one studies (36.2 %) were conducted in Germany, Switzerland/Germany, or Switzerland/Austria/Germany, k = 12 (20.7 %) in Sweden, k = 7 (12.1 %) in the USA, and k = 5 (8.6 %) in the Netherlands. Other studies were carried out in Australia (5.2 %, k = 3), the United Kingdom (5.2 %, k = 3), Canada (3.4 %, k = 2), Spain (3.4 %, k = 2), Denmark (1.7 %, k = 1), Japan (1.7 %, k = 1) or Switzerland (1.7 %, k = 1). The studies were published between 2008 and 2022.

Most of the included articles were RCTs that reported additional analyses of predictors/moderators within the primary outcome paper (37.9 %, k = 22) or as separately published secondary analyses of RCTs (44.8 %, k = 26). The study control groups included treatment as usual (TAU, 12.1 %, k = 7), waitlist (WL, 17.2 %, k = 10), psychoeducation (1.7 %, k = 3), active control groups (6.9 %, k = 4), attention control groups (3.4 %, k = 2), no treatment (1.7 %, k = 1), or a combination of WL control with other controls (i.e., WL and TAU (13.8 %, k = 8), WL and attention control (1.7 %, k = 1), WL and discussion forum (1.7 %, k = 1), and WL and psychoeducation (1.7 %, k = 1)). Seventeen studies (29.3 %) investigated three study conditions in total, including either a second control group or a second intervention group. Comparison interventions comprised other IMIs (64.7 %, k = 11), face-to-face treatments (29.4 %, k = 5; i.e., physical exercise or psychotherapy), and, in one case (5.9 %), cognitive–behavioral therapy (CBT) delivered via e-mail by a therapist. Two studies (3.4 %) analyzed data from a randomized factorial trial. Eight non-randomized studies (13.8 %) investigating treatment predictors with a pre–post design included only a single IMI treatment group. The majority of IMIs was CBT-based (78.3 %, k = 54). Other theoretical backgrounds included problem-solving therapy, psychodynamic therapy, and acceptance and commitment therapy; or, in some cases, different theoretical backgrounds were combined, or no information on the theoretical background could be identified. The sample sizes of the included studies ranged from $n = 13$ to $n = 1738$ participants. The total sample size of all included trials was $n = 12{,}813$. The mean age ranged between 21.6 and 62.9 years, and the percentage of men ranged from 0 % to 88 %.

Several studies targeted specific populations, including individuals with postpartum depression or physical comorbidity such as an HIV diagnosis, heart failure, epilepsy, diabetes, and chronic back pain. All studies used self-report assessments as a primary outcome measure. The Patient Health Questionnaire (Kroenke et al., 2001) was used in k = 27 studies (46.6 %), versions of the Beck Depression Inventory (Beck et al., 1961, 1996) in k = 12 studies (20.7 %), and versions of the Montgomery-Åsberg Depression Rating Scale (Montgomery and Åsberg, 1979; Svanborg and Åsberg, 1994) in k = 9 studies (15.5 %). Other outcome measures were the Center of Epidemiological Studies Depression Scale (Radloff, 1977), the Edinburgh Postnatal Depression Inventory (Cox

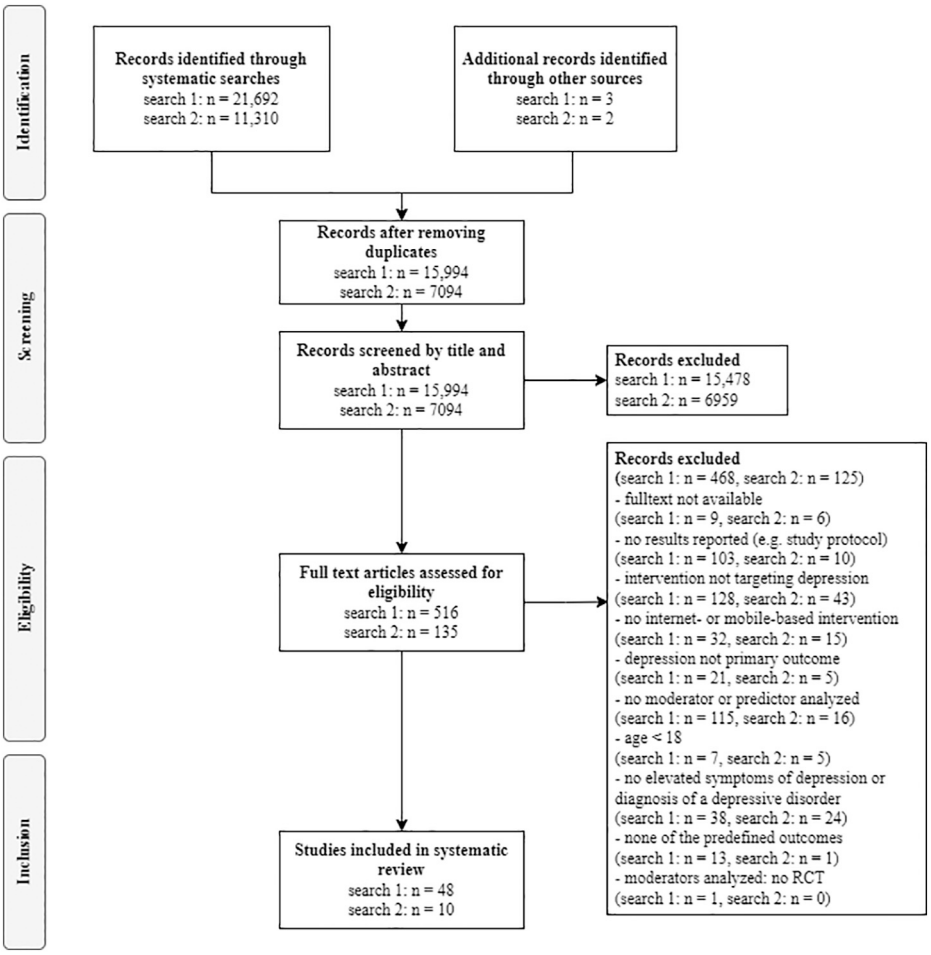

Fig. 1. PRISMA flow chart.

et al., 1987), the Hamilton Rating Scale of Depression (Hamilton, 1960), the Depression Anxiety Stress Scales (Lovibond and Lovibond, 1996), the Structured Clinical Interview for DSM-5 (First et al., 2016), and the Inventory of Depressive Symptomatology (Rush et al., 2000).

3.3. Characteristics of IPD meta-analyses

In addition to our systematic review of single studies, four IPD meta-analyses were identified from Cuijpers et al. (2022). One IPD meta-analysis included 13 studies on self-guided IMIs with symptom severity and response as outcomes ($n = 3876$), while another focused on response and remission outcomes of guided IMIs including 24 studies ($n = 4889$). Another IPD meta-analysis synthesized the findings of seven studies on subthreshold depression ($n = 2186$). Additionally, a network meta-analysis with 36 studies ($n = 8107$) assessed the strength of the association between the analyzed variables and the treatment outcome, without information on statistical significance. We further included two IPD meta-analyses on symptom deterioration as treatment outcome, which synthesized the findings from 18 studies ($n = 8107$) and 13 studies ($n = 3805$).

3.4. Predictors and moderators of treatment outcomes

Of the 58 single studies included, k = 7 (12.1 %) focused solely on moderator analyses, k = 14 (24.1 %) reported exclusively baseline-predictors, and k = 6 (10.3 %) solely investigated process-predictors. Fourteen studies (24.1 %) analyzed both types of predictors, while k = 17 (29.3 %) reported on predictors and moderators together. On average, m = 8 analyses on predictors/moderators were performed (range: m = 1–39).

In total, m = 466 analyses were extracted for baseline-predictors (59.7 %, m = 278), process-predictors (16.5 %, m = 77), and moderators (21.9 %, m = 102) of the treatment outcomes, while nine analyses (1.9 %) could not be assigned to any category (other). Among the analyses, the majority (67.4 %, m = 314) focused on predictors and moderators of symptom improvement, m = 99 (21.2 %) on symptom severity, m = 25 (5.4 %) on response, m = 18 (3.9 %) on remission, and m = 9 (1.9 %) on deterioration as outcomes. Predictor and moderator variables were categorized into the following 7 main categories and s = 40 subcategories: sociodemographic variables (s = 10), depression-related variables (s = 3), comorbidity (s = 4), intervention-related variables (s = 7), course-of-change variables (s = 1), variables related to other treatments (s = 4), and other (biopsychosocial) variables (s = 11).

Among all the included analyses of single studies, 74.0 % (m = 345) yielded nonsignificant results, 24.0 % (m = 112) reported significant results, and 1.9 % (m = 9) were inconclusive or lacking significance reporting. For analyses of moderators, 7.8 % (m = 8/102) were significant, while 25.2 % (m = 70/278) of baseline-predictor analyses and 40.3 % (m = 31/77) of process-predictors analyses were significant. From 6 IPD meta-analyses, m = 93 analyses could be extracted for 17 out of the 40 subcategories. Among these, 79.6 % (m = 74) were nonsignificant, 15.1 % (m = 14) were significant, and for 5.4 % (m = 5) no information on significance was available. Table 1 provides an overview of the findings for moderators, baseline-predictors, and process-predictors across categories.

Table 1
Results of extracted predictor/moderator analyses by category with global status of evidence.

Category	Number of studies	Total number of analyses	Number of analyses (% of total number of analyses)				Number of sign. analyses/total number of analyses (% sign. analyses)		Direction of association of predictor/moderator with treatment outcome (evidence from single studies)	Global status of evidence for category	Number of IPDs	Evidence from IPDs[a]
			Moderators	Baseline-predictors	Process-predictors	Unclear						
Sociodemographic variables												
Gender	27	37	9 (24.3 %)	27 (73.0 %)	–	1 (2.7 %)	3/37	(8.1 %)	Female: ↑ (3)	Insufficient	6	O (9)
Age	28	37	10 (27.0 %)	27 (73.0 %)	–	–	5/37	(13.5 %)	↑ (3); ↓ (1)	Insufficient	6	O (5); ↑ (4)
Educational level	15	19	5 (26.3 %)	14 (73.7 %)	–	–	4/19	(21.1 %)	Higher educational level: ↑ (4)	Insufficient	5	O (8); ↑ (1)[a]
Employment status	9	12	3 (25.0 %)	9 (75.0 %)	–	–	1/12	(8.3 %)	Working full time: ↑ (1)	Insufficient	5	O (8)
Relationship status	7	10	4 (40.0 %)	6 (60.0 %)	–	–	1/10	(10.0 %)	Being single: ↓ (1)	Insufficient	5	O (7), having a partner: ↑ (1)
Having children	3	4	1 (25.0 %)	3 (75.0 %)	–	–	0/4	(0 %)	–	Insufficient	–	–
Income level	3	3	–	3 (100 %)	–	–	1/3	(33.3 %)	Lower level income: ↑ (1)	Insufficient	–	–
Race	2	2	–	2 (100 %)	–	–	0/2	(0 %)	–	Insufficient	–	–
Living arrangements	2	2	–	2 (100 %)	–	–	0/2	(0 %)	–	Insufficient	–	–
Other sociodemographic variables	1	1	–	1 (100 %)	–	–	0/1	(0 %)	–	Insufficient	1	ethnic minorities: ↓ (2), O (2)
Depression-related variables												
Depression severity	29	37	9 (24.3 %)	28 (75.7 %)	–	–	23/37	(62.2 %)	↑ (17); ↓ (5); → (1)	Insufficient	6	O (5), ↑ (4)
History of depression	8	11	5 (45.5 %)	6 (54.5 %)	–	–	2/11	(18.2 %)	Fewer than five depressive episodes: ↑ (1); having a history of depression: ↑ (1)	Insufficient	1	O (4)
Depression diagnosis	5	12	3 (25.0 %)	9 (75.0 %)	–	–	2/12	(16.7 %)	Recurrent mild depressive episode: ↓ (1); dysthymia: ↓ (1)	Insufficient	–	–
Comorbidity									–			
Comorbidity (anxiety)	11	15	3 (20.0 %)	12 (80.0 %)	–	–	4/15	(26.7 %)	Diagnosis of panic disorder: ↓ (1); diagnosis of social anxiety disorder: ↓ (1); severity of anxiety symptoms: ↓ (2)	Insufficient	5	O (9)
Comorbidity (substance use)	3	7	3 (42.9 %)	4 (57.1 %)	–	–	1/7	(14.3 %)	Alcohol problems: ↓ (1)	Insufficient	1	O (4)
Comorbidity (other)	7	10	2 (20.0 %)	7 (70.0 %)	–	1 (10.0 %)	2/10	(20.0 %)	Diagnosis of personality disorder: ↓ (1); sleep problems: ↓ (1)	Insufficient	1	O (1)
Variables associated with comorbid physical disorders	3	11	8 (72.7 %)	3 (27.3 %)	–	–	2/11	(18.2 %)	Coping self-efficacy (related to HIV): ↑ (1); glucose level: ↓ (1)	Insufficient	1	O (1)
Intervention-related variables												
Adherence	12	19	–	–	17 (89.5 %)	2 (10.5 %)	7/19	(36.8 %)	↑ (7)	Insufficient	2	↑ (2), O (1)
Guidance	8	14	–	–	13 (92.9 %)	1 (7.1 %)	4/14	(28.6 %)	Time spent on guidance calls: ↓ (2); number of phone conversations: ↓ (1); receiving e-mail support ↑ (1)	Insufficient	2	O (2)
Internet-modality-related variables	5	5	1 (20.0 %)	4 (80.0 %)	–	–	2/5	(40.0 %)	Attitude towards psychological online interventions: ↑ (2)	Insufficient	–	–

(*continued on next page*)

Table 1 (*continued*)

Category	Number of studies	Total number of analyses	Number of analyses (% of total number of analyses)				Number of sign. analyses/total number of analyses (% sign. analyses)		Direction of association of predictor/moderator with treatment outcome (evidence from single studies)	Global status of evidence for category	Number of IPDs	Evidence from IPDs[a]
			Moderators	Baseline-predictors	Process-predictors	Unclear						
Expectations	5	5	1 (20.0 %)	2 (40.0 %)	2 (40.0 %)	–	1/5	(20.0 %)	↑ (1)	Insufficient	–	–
Therapeutic alliance	3	10	–	–	10 (100 %)	–	1/10	(10.0 %)	↑ (1)	Insufficient	–	–
Recruitment source	2	8	2 (25.0 %)	6 (75.0 %)	–	–	0/8	(0 %)	–	Insufficient	2	O (2)
Other intervention-related variables	3	4	1 (25.0 %)	–	3 (75.0 %)	–	0/4	(0 %)	–	Insufficient	–	–
Course-of-change variables												
Course-of-change variables	3	25	–	–	25 (100 %)	–	18/25	(72.0 %)	Early change in depression: → (7); early change in global distress: → (8); sudden gain in depression: ↑ (1); early change pattern (early response after screening): ↑ (1); early change pattern (early deterioration): ↓ (1)	Insufficient	–	–
Variables related to other treatments												
Concurrent medication	14	18	4 (22.2 %)	10 (55.6 %)	2 (11.1 %)	2 (11.1 %)	1/18	(5.6 %)	With medication: ↑ (1)	Insufficient	2	O (5)
Concurrent psychosocial treatment	7	7	–	3 (42.9 %)	2 (28.6 %)	2 (28.6 %)	2/7	(28.6 %)	With psychiatric or psychotherapeutic treatment: ↓ (1); with counseling services for mental health reasons: → (1)	Insufficient	–	–
Any concurrent treatment	2	3	1 (33.3 %)	1 (33.3 %)	1 (33.3 %)	–	0/3	(0 %)	–	Insufficient	–	–
Treatment history	8	11	3 (27.3 %)	8 (72.7 %)	–	–	4/11	(36.4 %)	Having a history of inpatient psychiatric care: ↓ (1); having a history of psychotropic medication: ↓ (1); no previous psychological therapy: ↑ (1); prior psychotherapy: → (1)	Insufficient	1	O (1)
Other (biopsychosocial) variables												
Cognitive variables	9	23	6 (26.1 %)	16 (69.6 %)	1 (4.3 %)	–	5/23	(21.7 %)	Negative automatic thoughts: ↑ (1); negative problem orientation: ↑ (1); vividness rating of training stimuli: ↑ (1); perceived usefulness of cognitive strategies: → (1); problem solving: → (1)	Insufficient	–	–
Behavioral variables	6	10	1 (10.0 %)	9 (90.0 %)	–	–	4/10	(40.0 %)	Avoidance: ↓ (1); behavioral activation: ↑ (2); exercise: ↑ (1)	Insufficient	–	–
Well-being/quality of life	5	9	1 (11.1 %)	8 (88.9 %)	–	–	1/9	(11.1 %)	Psychological well-being: ↑ (1)	Insufficient	–	–
Emotional variables	4	7	2 (28.6 %)	5 (71.4 %)	–	–	1/7	(14.3 %)	Emotional well-being: ↑ (1)	Insufficient	–	–
Social variables	4	8	1 (12.5 %)	7 (87.5 %)	–	–	4/8	(50.0 %)	Availability of social relationships: ↑ (2); social well-being: ↑ (1); social support: ↑ (1)	Insufficient	–	–
Negative life events	3	3	1 (33.3 %)	1 (33.3 %)	1 (33.3 %)	–	0/3	(0 %)	–	Insufficient	–	–
Distress/impairment	2	2	–	2 (100 %)	–	–	1/2	(50.0 %)	Global severity of psychopathology: ↓ (1)	Insufficient	–	–
Physical health	2	2	–	2 (100 %)	–	–	0/2	(0 %)	–	Insufficient	–	–
Biological variables	2	11	5 (45.5 %)	6 (54.5 %)	–	–	3/11	(27.3 %)	Right rACC volume: ↑ (1); right sgACC volume: → (1); total intracranial volume: → (1)	Insufficient	–	–
Personality	2	15	5 (33.3 %)	10 (66.7 %)	–	–	1/15	(6.7 %)	Neuroticism: ↑ (1)		–	–
Other	4	17	2 (11.8 %)	15 (88.2 %)	–	–	1/17	(5.9 %)	Having a family history of neuropsychiatric condition: ↓ (1)	Insufficient	–	–

IPDs = individual patient data meta-analyses; ↑ = significant predictor/moderator effect with higher scores/or specified category (of a categorical variable) associated with a better treatment outcome; ↓ = significant predictor/moderator effect with higher scores/or specified category (of a categorical variable) associated with a worse treatment outcome; → significant predictor/moderator effect but direction of association not further specified; O = no significant predictor/moderator effect; HIV = human immunodeficiency virus; rACC = rostral anterior cingulate cortex; sgACC = subgenual anterior cingulate cortex.

[a] Results of the network IPD meta-analysis (Karyotaki et al., 2021) are not reported within this table as they comprise results on the strength of the association between variables and treatment outcome and not on significant or nonsignificant effects.

3.5. Risk of bias and methodological quality of the included studies

The RoB assessment using the RoB 2 tool resulted in k = 34 single studies that raised some concerns (68.0 %), with k = 16 displaying a high RoB (32.0 %) and none displaying a low RoB (Fig. C.1, Appendix C). The RoB of non-randomized studies using the ROBINS-I tool resulted in an overall judgment of a moderate RoB for seven studies (87.5 %) and a serious RoB for one study (12.5 %; Table C.2, Appendix C). Regarding their methodological quality for assessing moderators and predictors, k = 1 study provided confirmatory evidence (1.7 %), k = 48 studies exploratory evidence (82.8 %), and 9 studies insufficient evidence (15.5 %; Table C.3, Appendix C).

3.6. Combined quality and global status of evidence of the variable categories

Regarding the combined overall quality of the studies included here, k = 34 studies (58.6 %) were rated as satisfactory, k = 24 studies (41.4 %) as unsatisfactory, and none of the studies (0.0 %) as having a good combined overall quality (Table C.4, Appendix C). Regarding the global status of evidence of predictors/moderators, all categories were classified as providing insufficient evidence (see Table 1). For almost all categories, <65 % of the analyses resulted in significant findings; thus, the requirements for moderate or strong evidence were not met. The analyses of variables related to the course-of-change alone resulted in a sufficient number of significant findings; however, because of the unmet remaining criteria this category had to be classified as providing insufficient evidence as well. Nevertheless, to identify variables with (potential) relevance for predicting treatment outcomes, we highlight findings on variables that display significant results in over 50 % of analyses, those with significant results in over 30 % of analyses and analyzed in more than five studies, and variables that yield significant results in IPD meta-analyses.

3.7. Sociodemographic variables

Sociodemographic variables as predictors/moderators of treatment outcomes were studied in k = 31 single studies with m = 127 analyses. Among these, 74.0 % (m = 94) examined baseline-predictors and 25.2 % (m = 32) moderators (other: 0.8 %, m = 1). The subcategories included gender (m = 37), age (m = 37), educational level (m = 19), employment status (m = 12), relationship status (m = 10), having children (m = 4), income level (m = 3), race (m = 2), living arrangements (m = 2), and domicile (m = 1). Most of these analyses (87.4 %, m = 111/127) from single studies yielded nonsignificant results. Results from all six IPD meta-analyses also were predominantly nonsignificant (76.5 %, m = 39/51). For all subcategories, except income level (significant analyses: 33.3 %, m = 1/3 from k = 3 studies), the proportion of significant findings in single studies was under 30 %. Significant results from IPD meta-analyses indicated a positive association with treatment outcomes for age (m = 4/10), educational level (m = 1/9), and having a partner (m = 1/9). A negative association within an IPD meta-analysis was found for ethnic minorities (m = 2/4).

3.8. Depression-related variables

Depression-related variables were analyzed in k = 30 single studies with m = 60 analyses. Most analyses (71.7 %, m = 43) focused on baseline-predictors, while 28.3 % (m = 17) explored moderators. These analyses encompassed the subcategories depression severity (m = 37), depression diagnosis (m = 12), and history of depression (m = 11). Of all analyses in single studies, 50.0 % (m = 30) yielded nonsignificant findings, 45.0 % (m = 27) were significant, and 5.0 % (m = 3) lacked information. Results from all six IPD meta-analyses were predominantly nonsignificant (64.3 %, m = 9/14). Only the subcategory depression severity exhibited a significant result proportion exceeding 50 %, with

62.2 % (m = 23/37) of k = 29 single studies and m = 4/10 significant results from IPD meta-analyses. The IPD network meta-analysis identified depression severity as the most important predictor of treatment outcome compared to the other investigated variables.

3.9. Comorbidity

Comorbidity was assessed in k = 15 single studies with m = 43 analyses. Most of the analyses (60.5 %, m = 26) were on baseline-predictors, and 37.2 % (m = 16) analyses were on moderators (other: 2.3 %, m = 1). The subcategories encompassed comorbidity of anxiety symptoms or diagnoses (m = 15), substance use (m = 7), other comorbidities (e.g., diagnosis of personality disorder, drug use, and sleep problems, m = 10), and variables associated with comorbid physical disorders (m = 11). Most of these analyses (79.1 %, m = 34/43) were nonsignificant. All analyses drawn from five IPD meta-analyses yielded nonsignificant results (100 %, m = 15/15). Across all subcategories, the proportion of significant results in single studies was <30 %.

3.10. Intervention-related variables

Intervention-related variables were studied in k = 29 single studies with m = 65 analyses, of which 69.2 % (m = 45) were on process-predictors, 18.5 % (m = 12) on baseline-predictors, and 7.7 % (m = 5) on moderators (other: 4.6 %, m = 3). Subcategories included adherence (m = 19), guidance (m = 14), variables related to the internet-based delivery of the intervention (e.g., computer knowledge, comfort with written communication, m = 5), expectations of the intervention (m = 5), therapeutic alliance (m = 10), recruitment source (m = 8), and other intervention-related variables (e.g., satisfaction with text messages, m = 4). Most analyses (72.3 %, m = 47/65) were nonsignificant. Results from all six IPD meta-analyses also were predominantly nonsignificant (71.4 %, m = 5/7). We found 36.8 % (m = 7/19) significant analyses of adherence as a process-predictor in k = 12 single studies and two significant analyses in one of two IPD meta-analyses. The significant results indicated a positive association of adherence with treatment outcomes.

3.11. Course-of-change variables

We identified m = 25 analyses of variables indicative of the course-of-change during the treatment (e.g., early change or sudden gain in depression) within k = 3 single studies. All of these were classified as process-predictors. The majority of the analyses yielded significant results (72.0 %, m = 18/25), with m = 7/25 (28.0 %) analyses being nonsignificant. None of the IPD meta-analyses examined course-of-change variables.

3.12. Variables related to other treatments

Variables related to other treatments (e.g., treatment history, medication) were analyzed within k = 19 single studies with m = 39 analyses. Among these, 56.4 % (m = 22) were on baseline-predictors, 12.8 % (m = 5) on process-predictors, and 20.5 % (m = 8) on moderators (other: 10.3 %, m = 4). Subcategories covered concurrent medication (m = 18), concurrent psychosocial therapy (e.g., psychotherapy, m = 7), any concurrent treatment (i.e., medication and psychosocial therapy or not specified, m = 3), and treatment history (m = 11). Most analyses (79.5 %, m = 31/39) were nonsignificant. One subcategory with a proportion of significant results larger than 30 % (36.4 %, m = 4/11) in k = 8 single studies was treatment history. All results from m = 3 analyses from two IPD meta-analyses were nonsignificant (100 %, m = 3/3).

3.13. Other (biopsychosocial) variables

Beyond the variables listed above, we identified other (biopsychosocial) variables studied in k = 21 single studies with m = 107 analyses. Most of these (75.7 %, m = 81) were on baseline-predictors, 22.4 % (m = 24) on moderators, and 1.9 % (m = 2) on process-predictors. Subcategories encompassed cognitive variables (m = 23), behavioral variables (m = 10), well-being/quality of life (m = 9), emotional variables (m = 7), social variables (m = 8), negative life events (m = 3), distress/impairment (m = 2), physical health (m = 2), biological variables (m = 11), personality (m = 15), and other variables (i.e., could not be categorized into one of the mentioned categories and were analyzed in only one study, m = 17). Most analyses (79.4 %, m = 85/107) showed nonsignificant findings. No results from IPD meta-analyses were available for this category. We found 40.0 % (m = 4/10) significant analyses in k = 6 single studies for the subcategory of behavioral variables such as behavioral activation or physical activity. The proportion of significant findings within the other subcategories was under 30 %, or they were analyzed in ≤5 studies.

4. Discussion

In this systematic review, we synthesized findings from 58 single studies (466 analyses) together with results from 6 IPD meta-analyses (93 analyses) concerning baseline- and process-predictors as well as moderators of treatment outcomes in IMIs for depression. None of the single studies was of good combined quality, and only one study met the criteria for confirmatory evidence, such as the pre-defined intention of testing predictors/moderators selected based on theory or evidence (Pincus et al., 2011). Most analyses focused on symptom improvement as the primary outcome and predictors instead of moderators of treatment outcome, with predominantly nonsignificant results. The variables primarily investigated across main categories and subcategories were sociodemographics, followed by depression severity, concurrent treatment, course-of-change, cognitive variables, and adherence. All variable categories were rated as providing insufficient evidence, and only depression severity and course-of-change variables showed more significant than nonsignificant results in single studies.

Higher baseline depression severity was found to be associated with better treatment outcomes in a large proportion of many analyses in single studies and IPD meta-analyses. Similar findings emerged from face-to-face psychotherapy studies for depression (Driessen et al., 2010; Whiston et al., 2019) and IMIs for related syndromes (Weisel et al., 2018). The results might imply that participants with more severe depressive symptoms at baseline benefit from IMIs for depression as effectively or even better as those with milder symptoms. However, it has to be considered that conclusions about depression severity as a predictor/moderator across its entire range are limited as many studies excluded participants with symptom severity below or above a cutoff score (e.g., PHQ-9 score 5–14 indicating mild to moderate symptoms as an inclusion criterion). Furthermore, the correlation of depression severity with treatment outcomes might be mediated by other variables (e.g., motivation, extent of engagement with an intervention). Moreover, regression to the mean, i.e., a higher probability of improvement for participants with a higher baseline symptom severity due to random error (Barnett et al., 2005), could explain the positive association between symptom severity and outcomes in pre-post studies. Overall, interpreting these findings requires caution, as significance also depends on the statistical power in the respective trial.

Course-of-change variables like early change or sudden gains demonstrated the highest proportion of significant outcomes and could be valuable indicators of participant benefit from IMIs. These findings are in line with those from other psychological interventions showing early response's impact on depression outcomes (Beard and Delgadillo, 2019). Also, for personalized care, assessing early changes and adapting ongoing treatments using progress feedback has been shown to be promising (de Jong et al., 2021; Lutz et al., 2015). However, course-of-change variables were analyzed in only three single studies and none of the IPD meta-analyses, offering very limited evidence compared to

other, more frequently analyzed categories.

Beyond depression severity and course-of-change variables, all other subcategories showed more than or equal to 50 % nonsignificant results. These large proportions of nonsignificant results might suggest that participants with varying characteristics may equally benefit from IMIs for depression. However, nonsignificant results from single studies must be interpreted cautiously as trials hardly ever are powered to detect significant effects of predictors/moderators (Brookes et al., 2004). Nonetheless, the included well-powered IPD meta-analyses also found large proportions of nonsignificant results and several variable categories without any significant findings from multiple analyses (i.e., gender, comorbidity, concurrent medication, employment status). However, it cannot be ruled out that these variables may be relevant, e.g., when considering other outcome domains (Chevance et al., 2020) or when analyzing more complex associations in combination with other predictive variables. Also the methodology used to assess predictors/moderators and outcomes, including the differentiation between self-reported and clinician-rated measures, could have an impact (Cuijpers et al., 2010). In our pursuit of identifying variables with potential relevance for predicting treatment outcomes, we additionally highlighted variables that were analyzed in over five studies and demonstrated significant results exceeding 30 %, as well as those that yielded significant outcomes in IPD meta-analyses.

Adherence was one of the variables commonly studied as process-predictor and a considerable proportion of significant results from single studies and IPD meta-analyses indicated that higher treatment adherence was associated with improved outcomes. Given that only about 53.5 % of participants complete an IMI for depression as recommended (Moshe et al., 2021), the role of adherence as a predictor is crucial. A systematic review on this topic shows that adherence measures vary widely between studies, and the operationalization of adherence (e.g., number of logins, completion of modules) might moderate its association with different treatment outcomes (Beintner et al., 2019; Donkin et al., 2011). Thus, the diversity in the assessment of adherence and outcomes across the included studies might explain the variability in our results with respect to significance.

Age emerged as a potentially influential factor, with certain studies indicating that older adults might derive greater benefits from IMIs than younger adults. In face-to-face therapy, age-related differences are mostly nonsignificant, with the exception of some evidence that the effect sizes are larger for younger adults compared with older adults (Cuijpers et al., 2020). The differences between the two modalities raise the possibility of age being a noteworthy moderator when comparing IMIs to face-to-face therapy, although this hypothesis lacks direct analysis in our research. Moreover, in practice, the treatment choice may depend not only on its effectiveness for a particular age group but also on patient treatment preferences, which in turn might be associated with age. Existing evidence indicates that younger adults might have stronger preferences for IMIs than older adults (Dorow et al., 2018; Eichenberg et al., 2013). Some results indicated that participants with higher education levels display more favorable treatment outcomes, possibly due to their familiarity with the presentation of textual material in IMIs, contrasting with those with lower education levels who might feel overwhelmed. However, motivation, volition, self-efficacy, or expectation of results may also play a crucial role beyond textual understanding as well as variations in self-help usage based on educational levels (Jorm et al., 2004). Significant results from an IPD meta-analysis indicated that ethnic minorities profit less from IMIs than native-born participants (Karyotaki et al., 2018a). Possible explanations include that interventions may need further cultural adaptation to be effective for these target groups or that outcome measures might underlie cultural bias (Bernal et al., 2009; Karyotaki et al., 2018a). Other results pointed to a significant association between relationship status and treatment outcomes, indicating a positive impact of having a partner. The importance of personal contact in the course of an IMI is shown in the superiority of guided over unguided interventions regarding their effectiveness and adherence (Moshe et al., 2021). The support of a partner might be helpful, e.g., in terms of motivation or integration of an IMI into everyday life, which in turn could enhance the intervention's effectiveness as seen in dyadic IMIs (Shaffer et al., 2020).

Some significant findings indicated that prior treatment might be unfavorable for the outcome of an IMI for depression. A possible explanation could be that an existing history of, e.g., inpatient care or medication, might indicate chronicity, recurrence, or therapy-resistance of depressive symptoms that might be more difficult to treat in general or with IMIs in specific. However, many other factors might play a role in the utilization of treatment for depression, such as attitudes towards seeking mental health treatment or sociodemographic variables like age and gender (Magaard et al., 2017; Mojtabai et al., 2016).

Behavioral variables, such as behavioral activation and physical activity, identified in (cognitive-)behavioral intervention studies also emerged as potentially relevant. The findings suggest that specific relevant predictors/moderators could be derived from the theoretical background of an intervention. As these variables may represent areas associated with depressive symptomatology, a similar effect to baseline depression severity could exist. Yet, the absence of IPD meta-analyses results and reliance on a limited number of single studies and their specific interventions curtail the generalizability and interpretation of these findings to other interventions.

4.1. Strengths and limitations

This systematic review established precise inclusion criteria to identify relevant studies on treatment outcome predictors and moderators in IMIs for depression. To ensure an inclusive overview, we encompassed not only RCTs but also studies with a pre-post study design. In complement to our systematic searches and for a thorough representation of the field's current status, we also identified pertinent IPD meta-analyses, offering higher statistical power than single trials (Cuijpers et al., 2022). Additionally, we evaluated both RoB and the methodological quality of the predictor/moderator assessment and synthesized the ratings into a combined quality measure for each study and a global status of evidence evaluation for each variable category.

This study also has several limitations. First, we included search terms indicative of “predictor” or “moderator,” potentially omitting relevant studies where such terms were not explicitly used in their title or abstract leading to a potential selection bias. Publication bias could lead to an overestimation of the proportions of significant results due to non-significant predictor or moderator effects not being published. Furthermore, in some studies we could not identify which variables exactly were nonsignificant as no further information on the variables tested were provided.

Second, we counted results on an analysis-level; therefore, sometimes including more than one result for one variable within one study, e.g., if a study analyzed a variable as a predictor and as a moderator, we counted two analyses for this variable. This may have affected our results, potentially leading to an overrepresentation of certain studies in specific variable categories. However, counting significant and nonsignificant results on a study-level by generating one result for each variable within a study resulted in similar findings.

Third, study characteristics that we did not consider in detail (e.g., method of outcome assessment) might be additionally important for interpreting our results, e.g., the type of control group may influence the results of a moderator analysis. The prediction of differential response to different interventions (e.g., IMIs compared to face-to-face therapy) is a crucial research question requiring a larger database. Addressing this question within our study was not possible due to the heterogeneity of the included studies and the variety of control conditions. Further details on these study characteristics and other potentially relevant factors are provided in Table C.1 in Appendix C.

Fourth, the categories used in this study were not derived from an established theoretical model or framework. They were formed

inductively considering all extracted variables as no model was available for this purpose. This approach led to the creation of some relatively broad categories depending on the scope of findings for the specific variables (e.g., course-of-change variables).

Fifth, studies were often designed and powered to detect the overall effect of an intervention on treatment outcomes; therefore, the mostly exploratory secondary analyses of moderators may not have been sufficiently powered to detect their effect on treatment outcomes (Brookes et al., 2004). Consequently, the absence of significant results might not imply an absence of association between the variables and treatment outcomes. The chosen statistical methods, and the application of significance levels (e.g., p-value $\leq$ 5 % or lower) in particular, also influence whether an effect is assessed as statistically significant (Benjamin et al., 2018). Furthermore, it is crucial not to conflate the statistical significance of a variable (i.e., quantification of the probability that the results are attributed to chance) with its actual clinical significance (i.e., the practical relevance of the effect; Ranganathan et al., 2015).

Sixth, our approach did not involve a systematic search of IPD meta-analyses, as these were identified via an existing review article on IPD meta-analyses on depression treatments (Cuijpers et al., 2022). We also did not conduct a RoB or quality rating for these publications.

Seventh, the criteria of the methodological quality rating of Pincus et al. (2011) were developed for evaluating moderator analyses and therefore not fully applicable for our research. Adaptions were necessary for analyses of predictors, especially process-predictors, of treatment outcome.

Eighth, despite all of the subcategories showing an insufficient global status of evidence, we discussed several variables as (potentially) relevant even if they had a proportion of significant results smaller than 50 %. The classification of the global status of evidence did not consider IPD meta-analyses and, therefore, only reflects the current state of research regarding single studies. Furthermore, criteria for assessing the global status of evidence relying on the proportion of significant results from single studies are problematic as most studies are not powered to detect significant predictor or moderator effects.

4.2. Future directions

In addition to our descriptive synthesis of multiple study results, further quantitative analyses are necessary to identify and confirm relevant variables for personalized care and examine the nature of their association with treatment outcomes. To detect moderator effects, confirmatory analyses based on studies fulfilling quality standards and sufficient power are needed. To fulfill this objective, studies should incorporate moderators chosen based on theories or existing evidence, accompanied by well-defined a priori hypotheses (Kraemer et al., 2006; Pincus et al., 2011). Moreover, to determine a clinically relevant moderating effect, studies focused on effect sizes and not p-values are needed (Kraemer, 2008; Kraemer et al., 2006). Further IPD meta-analyses would be useful to provide appropriate statistical power but also require the collection of similar variables for pooling across studies (Cuijpers et al., 2022).

Significant baseline- and process-predictors identified in this study warrant further investigation to determine whether they function as moderators (for baseline-predictors), mediators (for process-predictors) or non-specific predictors of treatment outcomes. For the purpose of personalized care, more complex associations and interactions between multiple relevant predictors/moderators should also be considered, as analyzed in one IPD network meta-analyses so far (Karyotaki et al., 2021). Moreover, studying moderators and non-specific predictors in combination with mediators and mechanisms of change may unveil processes underlying the differential moderator effects on treatment outcomes, identifying significant moderators, and informing mediator research (Domhardt et al., 2021; Huibers et al., 2021). Research on process-predictors, such as course-of-change variables (e.g., early change), might present a promising approach to identify differential treatment responses. Even if treatment has already started at the time of variable measurement, understanding the association of process-predictors with outcomes may guide adaptions of ongoing interventions, e.g., according to a specific pattern of change, early in treatment (Lutz et al., 2009). Further, knowledge on significant predictors and moderators of treatment outcomes could help to reveal promising adaptions of existing interventions, e.g., by cultural adjustments (Spanhel et al., 2021), in order to improve treatment outcomes for specific subgroups.

For a comprehensive understanding of who benefits from an IMI, potentially distinct from on-site treatment, greater attention should be paid to previously understudied variables. Participant characteristics related to the delivery modality, e.g., eHealth literacy (Norman and Skinner, 2006a, 2006b), attitude towards online interventions (Schröder et al., 2015, 2018), and other "digital factors" such as the digital working alliance or outcome expectations regarding a specific device (Domhardt et al., 2021) might serve as relevant moderators in IMIs versus other non-internet-based interventions. A comparison between characteristics of patients who actively decide to use an IMI and characteristics of patients who prefer other treatment options could uncover variables with the potential of being a baseline-predictor/moderator of IMI treatment success to inform treatment allocation. Given that depression severity stands as the most evident predictor, it might be advisable to discourage the exclusion of severely depressed participants from IMIs. Instead, the research emphasis should be directed towards elucidating the connections between depression severity and treatment outcomes, as well as enhancing interventions for individuals with milder levels of depression. Furthermore, future investigations should dedicate greater attention to different outcomes. As treatment adherence might be a relevant outcome predictor, and noncompliance with treatment is high in IMIs (Moshe et al., 2021), predictors of adherence itself, as well as of treatment engagement (e.g., behavioral change in everyday life), should be further investigated. In particular, more research on predictors/moderators of symptom deterioration (Ebert et al., 2016; Karyotaki et al., 2018b) and other negative effects in IMIs (Rozental et al., 2015) is essential to provide precise intervention recommendations and enhance the safety of their application.

4.3. Conclusion

Our review showed that the overall global status of evidence from single studies for predictors and moderators of IMIs for depression is insufficient to draw firm conclusions for personalized treatment recommendations. In contrast, IPD meta-analyses focused on well-studied variables such as sociodemographics and baseline depression severity, providing more robust evidence for their effect on treatment outcomes. Overall, baseline depression severity showed a strong predictive value, and process-variables such as early change showed great potential in predicting treatment outcomes. Other potentially relevant variables with significant results and need for further investigation include adherence, age, educational level, ethnicity, relationship status, treatment history, and behavioral variables. However, while many nonsignificant results imply that several commonly analyzed variables might not be relevant in personalized care and IMIs might be effective across participants with varying characteristics, insufficient statistical power in exploratory single studies could also contribute to non-significance, and variables that account for existing differential treatment effects still need to be identified. Future research should target so far understudied variables (e.g., content- and delivery-specific variables) and precisely characterize the nature of their associations with treatment outcomes and variable types (non-specific predictor, moderator, mediator).

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CRediT authorship contribution statement

All authors contributed to the design of the study. T.S. and M.S. conducted the systematic searches, screening, data extraction, and ratings of risk of bias and methodological quality. T.S. and A.Z. drafted the manuscript. All authors (T.S., M.S., H.B., P.C., D.E., and A.Z.) contributed to the further writing and approved the final manuscript.

Declaration of competing interest

A.Z. reports fees for presentations at scientific meetings and for expert videos for an internet-based intervention. D.E. has served as a consultant to/on the scientific advisory boards of Sanofi, Novartis, Minddistrict, Lantern, Schoen Kliniken, Ideamed, and German health insurance companies (BARMER, Techniker Krankenkasse) and a number of federal chambers for psychotherapy. He is also a stakeholder in the institute for health training online (formerly GET.ON, now HelloBetter), which aims to implement scientific findings related to digital health interventions in routine care. H.B. reports to have received consultancy fees, fees for lectures or workshops from chambers of psychotherapists and training institutes for psychotherapists and license fees for an Internet-intervention. P.C., T.S., and M.S. report no conflicts of interest.

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Appendix A. Supplementary data

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