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Psychological treatment of depression: A systematic overview of a 'Meta-Analytic Research Domain'

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ABSTRACT

Background: Over the past 16 years, we have developed a 'Meta-analytic Research Domain' (MARD) of all randomized trials of psychological treatments of depression. A MARD is a living systematic review of a research field, that cannot be otherwise covered by one (network) meta-analysis and includes multiple PICOs. In this paper we give an overview of the findings of this MARD.
Methods: A narrative review of the results of the 118 meta-analyses on psychotherapies for depression that were published within our MARD.
Results: Most research has been conducted on cognitive-behavioral therapy (CBT), but several other psychotherapies are also effective, with few differences between therapies. They can be effectively delivered in individual, group, telephone and guided self-help format and are effective in many different target groups and across different age groups, although the effects are significantly smaller in children and adolescents. Psychotherapies have comparable effects as pharmacotherapy at the short term but are probably more effective at the longer term. Combined treatment is more effective than either psychotherapy or pharmacotherapy alone at the short, but also at the longer term.
Limitations: We did not summarize all published meta-analyses (protocols, methodological studies) and have not compared our results to those found in other meta-analyses on comparable subjects.
Conclusion: Psychotherapies can contribute considerably to a reduction of the disease burden of depression. MARDs are an important next step in the aggregation of knowledge from randomized controlled trials in psychological treatments of depression as well as in other healthcare sectors.

1. Introduction

About 280 million people worldwide suffer from a depressive disorder (WHO, 2022). These disorders are associated with considerable suffering by patients and their families, increased mortality and morbidity (Cuijpers et al., 2014a), and enormous economic costs (König et al., 2020). In addition, they are the second leading cause of years lived with disability on the population level (WHO, 2022). Next to pharmacotherapy, psychotherapy is the first-line treatment of depressive disorders. The effects of psychotherapies have been examined in >850 randomized controlled trials (RCTs), examining many different types of psychotherapy, across all age groups, in various settings, for many different target groups, with all kinds of control conditions, in varying lengths, and in several different treatment formats, including individual,

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group, telephone-based, and (guided and unguided) digital formats. Many of these trials have also compared different types of psychotherapies with each other, as well as with pharmacotherapy and combined treatment. Because of the large number of RCTs with all these different comparisons, target groups and interventions, this body of research cannot be covered by one meta-analysis. To get a comprehensive overview of what is known about the effects of these interventions, an extensive series of meta-analyses is needed.

We have proposed to step up to a next level of aggregation of individual RCTs, when the number of trials is large and cover several different comparisons, types of treatment and target groups (Cuijpers et al., 2022a). A 'Meta-analytic Research Domain' (MARD) is a living systematic review of a field of research that cannot be covered by a single (network) meta-analysis as it includes multiple PICOs (Participants, Interventions, Comparators, Outcomes). MARDs provide a next-level aggregation of outcomes of RCTs, because they keep track of developments in the field, use consistent methods, cover all sub-areas of the domain (not only the ones that are included in published meta-analyses) and are constantly updated (Cuijpers et al., 2022a). A MARD has several advantages over conventional living systematic reviews and umbrella reviews, including the use of a consistent methodology across all individual meta-analyses that are published within the MARD (e.g., study inclusion, data extraction, synthesis of results), the possibility to examine secondary outcomes and perform rapid meta-analyses on new developments.

A MARD is comparable to an umbrella review in the sense that it covers all research in a specific research domain (Cuijpers et al., 2022a, 2022b). However, a MARD has several advantages over umbrella reviews. First, a MARD is a living systematic review that is updated regularly, while most umbrella reviews are not regularly updated. Second, the delay of including studies in a MARD is smaller than in an umbrella review (because this has the delay of including reviews, which in turn have their own delay of including single studies). Third, a MARD has a consistent methodology across all subfields within the research domain, while umbrella reviews include different reviews with varying methodologies. Fourth, umbrella review themselves can follow different methodologies. To date there is no univocal consensus on how data should be analyzed to assess the quality of evidence in umbrella reviews. Such heterogeneity of approaches is also reflected in the vast array of terms used as synonyms for "umbrella review", i.e., "reviews of reviews", "overviews of (systematic) reviews", "meta-reviews". Finally, an umbrella review relies on existing reviews, which may not cover a full field, while in a MARD all relevant studies are included, leaving no open spaces. In the past 16 years, we have developed a MARD on psychological treatments of depression. We have previously described the methods and development of this MARD over time (Cuijpers et al., 2008, 2011a; Cuijpers, 2017; Cuijpers et al., 2022a). However, the last systematic overview of the published meta-analyses within this MARD was published >5 years ago and several important new meta-analyses have been published since then. It is time, therefore, to provide an updated overview of the meta-analyses that have been conducted within the MARD. Because our MARD includes all RCTs on psychological treatments of depression, the current systematic review of meta-analyses gives an overview of all the knowledge that can be collected from RCTs on these psychological treatments.

The aim of the current paper is to give an overview of the main findings from the meta-analyses that have used the data from our MARD, including randomized controlled trials of psychological treatments of depression, regardless of the type of psychological intervention, type of depression, age group, target group or comparator. First, we give an overview of the effects of psychotherapies compared to control groups, and focus on the outcomes in general, differential effects between different psychotherapies, longer-term effects, and secondary outcomes. Second, we focus on the outcomes related to characteristics of patients and of interventions. Third, we describe the results of the meta-analyses comparing psychotherapy with antidepressants and combined treatments. Fourth, we summarize the results of individual patient-data (IPD) meta-analyses. Finally, we will describe what has been learned about negative effects, especially deterioration.

2. Methods

2.1. Identification and selection of studies

The methods of building the database of RCTs, extracting the data, and conducting the meta-analyses have been published elsewhere (Cuijpers et al., 2008, 2022b; Cuijpers and Karyotaki, 2020) and are available on the website of the project (www.metapsy.org). In brief, every 4 months we conduct systematic searches in PubMed, PsychINFO and Embase to identify RCTs comparing any psychological treatment of depression in any format, in any target group, to any comparator (control, pharmacotherapy, combined treatment, another psychotherapy, another treatment format, etc.). After removing duplicates, all identified records are read by two independent researchers and if one of them decides that a paper may meet the inclusion criteria, the full text of the paper is retrieved. All full-text papers are read again by two independent researchers and the decision to include is made in consensus or after consulting a third researcher.

The included studies are categorized into one of 4 main categories: (1) psychotherapy versus control; (2) psychotherapy versus pharmacotherapy and combined treatment; (3) psychotherapy versus other psychotherapies; and (4) other comparisons (with several smaller and more specific subcategories, such as inpatient settings, unguided treatments, or dismantling studies). The number of trials in each of these (sub)categories can be found in the recent methods paper of this project (Cuijpers et al., 2022b). Psychotherapy is defined as "the informed and intentional application of clinical methods and interpersonal stances derived from established psychological principles for the purpose of assisting people to modify their behaviors, cognitions, emotions, and/or other personal characteristics in directions that the participants deem desirable" (Campbell et al., 2013).

2.2. Data extraction

After inclusion of a study, five categories of data are extracted: (1) characteristics of the participants in the study (target group; mean age; proportion of women; type of recruitment); (2) characteristics of the interventions (type of therapy; treatment format, number of sessions); (3) general characteristics of the study (publication year; characteristics of the comparator; country where the study was conducted); (4) risk of bias; and (5) data to calculate effect sizes. Risk of bias is assessed in most meta-analyses using four items from the Cochrane risk of bias tool, version 1 (Higgins et al., 2011): sequence generation, allocation concealment, blinding of outcome assessors, and intention-to-treat analyses. Details and definitions of these characteristics are given elsewhere and can be found at the website of the project (www.metapsy.org).

2.3. Main outcome

For the calculation of effect sizes, we use a hierarchy, with a preference for effect sizes based on mean (M), standard deviation (SD) and *N* at post-test, followed by change scores (with SD of change and *N*), binary outcomes, and if none of these are reported, we use other statistics (*t*-value, *p*-value, etc.) to calculate the effect sizes. Depressive symptomatology is the primary outcome, but for specific meta-analyses we also extract secondary outcomes, like for example quality of life, social support, anxiety, etc.

Hedges' *g* indicating the difference between therapy and comparator is used as the main outcome. In most meta-analyses, effect sizes are pooled within studies before they are pooled across studies. Effect sizes of 0.8 can be assumed to be large, while effect sizes of 0.5 are moderate, and effect sizes of 0.2 are small (Cohen, 1988). An effect size of 0.24 has been proposed as a clinically meaningful threshold (Cuijpers et al., 2014b).

In some meta-analyses, we have also calculated response (i.e., 50 % symptom reduction from baseline symptoms) and other binary outcomes, such as remission and clinical significant change. In these studies, we have calculated the rates separately for the treatment and control condition but also calculated the relative risk of a positive outcome of the treatment compared to the control group. In these studies, we also calculated the number needed-to-treat (NNT), indicating how many patients need to be treated to achieve one more positive outcome (1 divided by the risk difference between treatment and control). In some studies, we also calculated negative outcomes (deterioration) and the number needed to harm (NNH; the equivalent of the NNT for negative outcomes).

2.4. Meta-analyses

In all meta-analyses we pooled the individual effect sizes according to the random effects model. We calculated the level of heterogeneity with I^2 and its 95 % confidence interval (CI). In all meta-analyses, we also examined small-study effects (usually considered to be an indicator for publication bias), by examining the asymmetry of the funnel plot (showing that small studies with large effect sizes are more likely to be published than small studies with small or negative effect sizes). All meta-analyses were conducted either with Comprehensive Meta-analysis software, and in recent years with the "meta" (Balduzzi et al., 2019), "metafor" (Viechtbauer and Cheung, 2010), and "dmetar" (Harrer et al., 2019) packages in R.

Recently, we have updated and extended the methods for conducting meta-analyses and have developed "metapsyTools", an R package to support these analyses. We have added functions to prepare and check the extracted data, and to run a series of sensitivity analyses and additional analyses for examining publication bias, to generate descriptive tables, as well as tables for the main outcomes and subgroup analyses. More information can be found at the documentation page of the package (tools.metapsy.org).

2.5. Published meta-analyses and summary of outcomes

We have published several types of meta-analyses using the data from our database. Most are conventional meta-analyses, in which pairwise comparisons were examined. However, we also published several network meta-analyses in which both direct and indirect comparisons were examined simultaneously. In addition, for some comparisons, we have also conducted "individual participant data" (IPD) meta-analyses, in which the primary data of trials examining a comparison are collected, which allows to examine predictors of outcome at the patient level.

3. Results

3.1. Included studies and published meta-analyses

The flowchart for the inclusion of studies up to January 1, 2022 is given in a recent methods paper which we wrote about the project (Cuijpers et al., 2022b). In total, 878 RCTs were included in the database: 438 trials compared psychotherapies with control groups, 130 compared two psychotherapies with each other, 116 compared psychotherapy with pharmacotherapy or combined treatment, and 259 examined other comparisons of psychotherapies (for the details and the numbers in subcategories, see Cuijpers et al., 2022b).

The number of trials that meet inclusion has increased considerably over time. In Fig. 1, we have given a cumulative overview of the included trials over the years and separately across different regions. As can be seen, up to the mid 1990s almost all research was done in North America, since then a growing number of trials has been done in Europe (including the UK) and since 2005 research in other countries (mostly

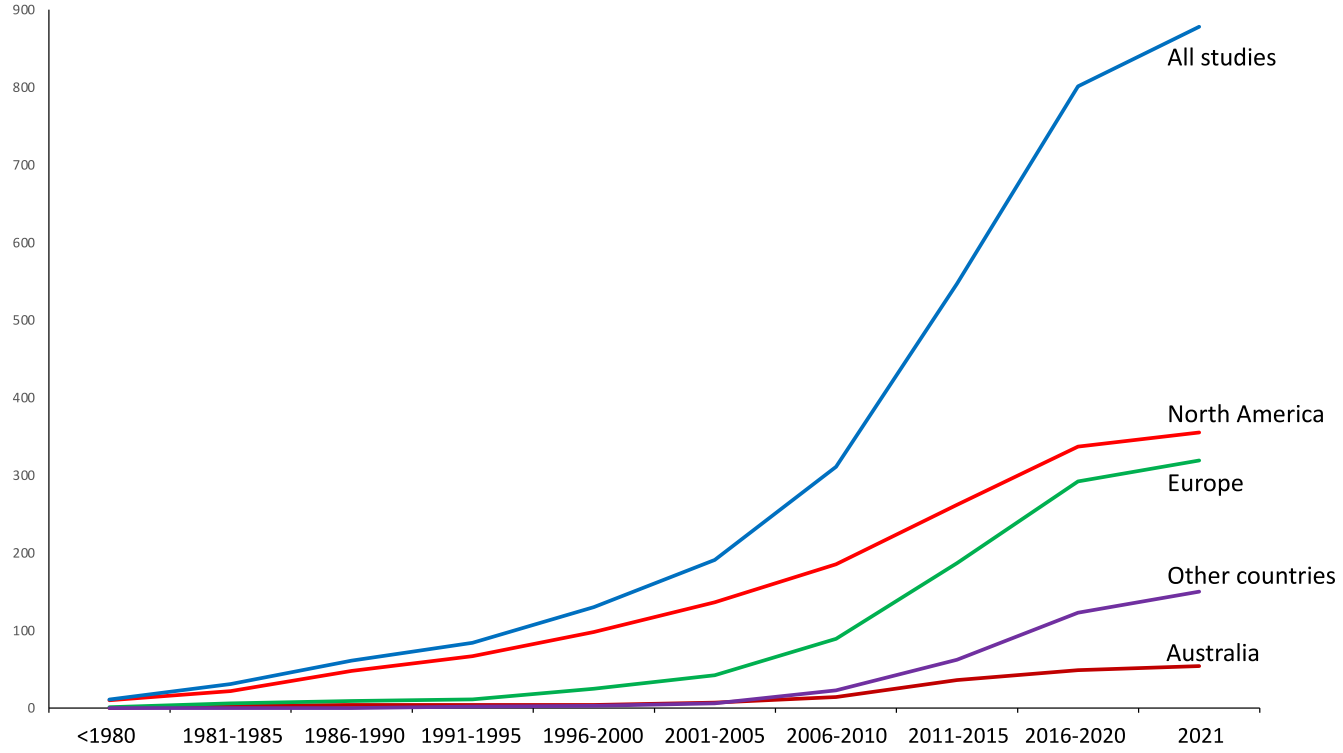

Fig. 1. Cumulation of RCTs on psychotherapy for depression across different regions over time.

Table 1
The effects of different types of psychotherapy for depression, treatment format, amount, frequency and intensity of treatment.

Main type (subtypes)	*k*	*g*	95 % CI	I^2	95 % CI	
Types of therapy versus any control						
Cognitive behavior therapy	205	0.73	0.65; 0.80	80	77; 82	Cuijpers et al., 2020b
- Beck	37	0.95	0.77; 1.14	68	53; 76	
- Coping with Depression	26	0.38	0.27; 0.49	38	0; 61	
- GSH: Burns	7	0.97	0.62; 1.32	39	0; 73	
Behavioral activation therapy	21	1.05	0.80; 1.30	77	65; 84	
- Pleasant events	7	1.04	0.77; 1.30	0	0; 58	
- Contextual	7	1.06	0.46; 1.65	87	74; 92	
Problem-solving therapy	30	0.75	0.53; 0.97	87	82; 90	
- Extended	8	1.07	0.50; 1.63	88	78; 92	
- Brief	14	0.81	0.42; 1.19	90	86; 93	
- Self-examination therapy	8	0.42	0.21; 0.64	63	0; 81	
Third wave therapies	19	0.85	0.63; 1.07	75	59; 83	
- ACT	8	0.74	0.61; 0.87	0	0; 56	
- MBCT	7	0.71	0.41; 1.01	58	0; 80	
Interpersonal psychotherapy	27	0.60	0.34; 0.86	87	82; 90	
- Full	14	0.57	0.31; 0.83	77	58; 85	
- Brief	13	0.64	0.13; 1.15	91	87; 94	
Psychodynamic therapy	12	0.39	0.16; 0.62	70	37; 82	
Non-directive supportive therapy	19	0.58	0.42; 0.75	45	0; 67	
Life-review therapy	14	1.10	0.68; 1.51	89	83; 92	
Format (care as usual as comparator)						
• Individual	30	0.52	0.39; 0.65	51	18; 67	Cuijpers et al., 2020b
• Group	21	0.83	0.54; 1.12	88	84; 91	
• Telephone	6	0.63	0.19; 1.07	87	71; 92	
• Guided self-help	8	0.56	0.30; 0.82	79	52; 88	
• Unguided self-help	9	0.14	−0.02; 0.29	57	0; 78	
Number of sessions						Cuijpers et al., 2013c
• 4–6	23	0.47	0.30; 0.65	45	9; 66	
• 7–10	27	0.58	0.42; 0.74	69	55; 79	
• 12–16	22	0.68	0.50; 0.85	57	30; 73	
• 18–24	20	0.61	0.41; 0.81	42	1; 66	
Sessions per week						Cuijpers et al., 2013c
• <1	10	0.44	0.19; 0.69	64	29; 82	
• 1	46	0.58	0.46; 0.70	53	35; 67	
• >1	22	0.71	0.52; 0.91	53	24; 71	

Australia and East Asia) is increasing.

Over the past 16 years, we have published 118 meta-analyses using the data from this database of RCTs, with on average 7 papers per year (ranging from 17 in 2021 to 2 in 2012; excluding the one meta-analysis in 2006). The majority (85; 72 %) of these 118 papers were conventional pairwise meta-analyses, 18 were IPD meta-analyses (15 %), 9 were network meta-analyses (8 %), and the remaining 6 were protocols for meta-analyses (5 %). Seventy-three of the 118 papers (62 %) are cited and described in the present narrative review. The others are either protocols (5), focused on methodological issues that go beyond the scope of the current paper (19; 16 %), were older meta-analyses for which updates were available that are cited in the text (14; 12 %) or were not included for other reasons (3; 3 %).

The references of the published studies are given in Appendix A. In this Appendix we also report for each meta-analysis the year of publication, whether it is cited in the current text, the paragraph in which it is described, or the reason for not including it in the text.

3.2. The effects of psychotherapies compared to control conditions and to each other

There are 8 main types of psychotherapy that have been compared to control conditions in 10 or more RCTs (Table 1; Cuijpers et al., 2020b): Cognitive behavior therapy (CBT), behavioral activation therapy, problem-solving therapy, interpersonal psychotherapy, brief psychodynamic therapy, non-directive supportive counseling, life-review therapy, and 'third wave' psychotherapies (which include acceptance and commitment therapy, mindfulness-based cognitive therapy, metacognitive therapy and others). The effect sizes for these main psychotherapies range from g = 0.39 for psychodynamic therapy to g = 1.10 for life review therapy. For several psychotherapies, more specific subtypes using a specific manual are examined in at least 5 RCTs (Table 1).

Over the years, we have conducted a series of meta-analyses examining the effects of specific psychotherapies, including CBT (Cuijpers et al., 2013a, 2016a), problem-solving therapy (Cuijpers et al., 2007; Cuijpers et al., 2018d), interpersonal psychotherapy (Cuijpers et al., 2011b, 2016b), psychodynamic therapies (Driessen et al., 2010; Driessen et al., 2015), non-directive supportive counseling (Cuijpers et al., 2012), the 'Coping with Depression' course (Cuijpers et al., 2009a) and behavioral activation (Cuijpers et al., 2007; Ekers et al., 2014). The effects and differential effects of therapies can, however, better be examined in network meta-analyses in which all direct and indirect evidence is integrated into one big analysis. Building on a previous network meta-analysis (Barth et al., 2013), we conducted a large network meta-analysis of 331 RCTs comparing these 8 psychotherapies with each other or with usual care, waitlist, or pill placebo (Cuijpers et al., 2021a). We found no significant differences between psychotherapies in term of efficacy in reducing depressive symptoms. The only exception was non-directive supportive counseling, which was effective, but significantly less than other psychotherapies. This may, however, be an artefact, because counseling is often used as a control condition for other psychotherapies, and therefore delivered under sub-par conditions. CBT is by far the best examined type of psychotherapy (more than half of the controlled trials have focused on it; Cuijpers et al., 2020b), but there is no indication that it is more or less effective than other psychotherapies.

The methodological problems of the RCTs comparing psychotherapies with control conditions and with each other are considerable. Of the 331 RCTs in the large network meta-analysis, only 31 % met all criteria for low risk of bias. In addition, the risk for publication bias was

high in all meta-analyses comparing psychotherapies with control conditions. After adjustment for risk of bias and for publication bias, the effect sizes are typically still significant, but considerably smaller compared to the overall analyses in which these problems are not taken into consideration. A complication of this body of research is also that heterogeneity is high in most analyses. This makes it more difficult to demonstrate the robustness, generalizability, and clinical applicability of findings. Despite these problems, which are not very different from what happen for other treatments in the biomedical field, it seems safe to conclude that psychotherapies are effective and that there are no major differences between most major types of psychotherapy in the treatment of people suffering from depression.

Because effect sizes such as Hedges' *g* are difficult to interpret from a clinical perspective, we conducted a meta-analysis of absolute outcomes of psychotherapies and control conditions (Cuijpers et al., 2021b; building on a previous study, Cuijpers et al., 2014c). Response (50 % reduction of depression symptomatology at study endpoint), remission (HAMD-D < 7 at study endpoint) and deterioration rates (Reliable Deterioration Index) were extracted from the 228 included RCTs (with 23,574 patients) or were estimated with the baseline mean and post-test mean, standard deviation (SD) and number of participants (*N*), using a validated imputation method (Furukawa et al., 2005). The overall response rate in psychotherapies was 41 %, 17 % for usual care and 16 % for waitlist. No significant differences between types of therapy were found. About one third of patients remitted after therapy compared with 9 % to 12 % in control conditions.

We conducted a comparable study on response and remission in children and adolescents (Cuijpers et al., 2021c). We found an overall response rate of 39 % in the treatment and 24 % in the control conditions (NNT = 6.2). Clinically significant improvement was found in 54 % of youth in therapy, compared with 32 % in control groups (NNT = 5.3).

The effects of psychotherapies are significant up to 12 (± 6) months after baseline. Building on earlier meta-analyses on longer-term outcomes of psychotherapies (Karyotaki et al., 2016a, 2016b), we found a significant effect for CBT, behavioral activation therapy, problem-solving therapy, interpersonal psychotherapy, and psychodynamic therapy compared with care-as-usual (Cuijpers et al., 2021a). There were some indications that problem-solving may be somewhat more effective than other psychotherapies at follow-up.

3.3. Secondary outcomes

Change in depressive symptoms is the main outcome for most trials on psychotherapy for depression. However, we have also conducted a series of meta-analyses in which we examined the effects of psychotherapy on secondary outcomes. In these meta-analyses, we found that psychotherapy for depression is also effective on quality of life, social functional, social support, anxiety, hopelessness, dysfunctional thinking, positive and negative affect (Table 2; Kolovos et al., 2016; Renner et al., 2013; Park et al., 2014; Cristea et al., 2015; Boumparis et al., 2016; Weitz et al., 2018). There is also a small group of studies on psychotherapy in depressed mothers, which shows that psychotherapy also has a significant effect on mental health in their children, strengthening mother-child interaction and parental functioning (Cuijpers et al., 2015a). Meta-regression analyses typically show that these secondary outcomes are significantly associated with the effects on depression.

In a meta-analysis of RCTs examining the effects of psychotherapy for depression on suicidality we identified only 4 trials, which resulted in a small, non-significant effect size (Cuijpers et al., 2013b). This finding should be considered with caution, because statistical power was low, and the study is relatively old. A rough check indicated that the number of trials has increased considerably, but these have not yet been pooled and the outcomes have not yet been published.

There are also some studies in patients with diabetes and depression, in which the effects of therapy on glycemic control were examined (Miguel et al., 2021; Cristea et al., 2019). The effects on glycemic control were not significant (Table 2). In patients with general medical disorders no significant effects on pain (7 studies) and on mortality (12 studies) were found (Miguel et al., 2021), possibly because of low power. Another set of studies examined the effects of therapies on cortisol, but also found no significant association (Cristea et al., 2019).

Table 2
Secondary outcomes.

Outcome	*k*	*g*	*95 % CI*	I^2	*95 % CI*	
Quality of life	31	0.33	0.24; 0.42	21	0; 49	Kolovos et al., 2016
Social functional	39	0.46	0.32; 0.60	71	58; 78	Renner et al., 2013
Social support	15	0.38	0.29; 0.48	0	0; 54	Park et al., 2014
Anxiety	52	0.52	0.44; 0.60	55	40; 60	Weitz et al., 2018
Suicidality	4	0.12	−0.20; 0.44	31	0; 77	Cuijpers et al., 2013c
Hopelessness	18	1.10	0.72; 1.48	77	62; 84	Cuijpers et al., 2013c
Dysfunctional thinking	21	0.51	0.39; 0.62	6	0; 45	Cristea et al., 2015
Positive affect	8	0.37	0.13; 0.60	39	0; 73	Boumparis et al., 2016
Negative affect	8	0.40	0.31; 0.68	73	44; 87	Boumparis et al., 2016
Mental health in children	7	0.40	0.22; 0.59	1	0; 71	Cuijpers et al., 2015a
Mother-child interaction	8	0.35	0.17; 0.52	0	0; 68	Cuijpers et al., 2015a
Parental functioning	5	0.67	0.30; 1.04	51	0; 82	Cuijpers et al., 2015a
Glycemic control (diabetes)	10	−0.01	−0.22; 0.21	75	53; 87	Miguel et al., 2021
Cortisol concentration	5	−0.19	−0.45; 0.06	0	0; 71	Cristea et al., 2019
Pain (in general medical patients)	7	0.13	−0.21; 0.47	53	0; 80	Miguel et al., 2021
Mortality (OR)	12	(0.75)	(0.44–1.29)	32	0; 67	Miguel et al., 2021

3.4. Characteristics of the interventions

Apart from the type, outcomes may also be related to other characteristics of the psychotherapies, including delivery format, the amount, frequency, and intensity of the sessions.

We conducted a large network meta-analysis on delivery format in CBT for depression (Cuijpers et al., 2019a), including individual, group, telephone based, guided self-help (mostly internet-delivered therapies) and unguided self-help (also mostly internet-delivered). The meta-analysis included 155 trials (11,000 participants) comparing formats with each other or with usual care, waitlist, or pill placebo. No significant differences between individual, group, telephone-delivered and guided self-help were found, although drop-out from the study was significantly higher in guided self-help (see also Van Ballegooijen et al., 2014; Table 1). This meta-analysis builds on several earlier meta-analytic studies showing that treatment format is not related to the outcomes, if there is human support (Cuijpers et al., 2011c; Karyotaki et al., 2017; Karyotaki et al., 2018a, 2018b). IPD meta-analyses have shown that unguided internet-interventions also have small, but significant effects, although these are smaller than those of face-to-face and guided self-help interventions (Karyotaki et al., 2017, 2021).

In an earlier meta-analysis, we examined whether the amount, frequency, and intensity of therapy was related to the effect sizes (Cuijpers et al., 2013c). In this meta-analysis we only included studies on individual therapies. We found only a small association between number of

Table 3
Characteristics of participants at the study level.

	k	*g*	*95 % CI*	I^2	*95 % CI*	
Age groups						
• Children (<13 years)	15	0.35	0.15; 0.55	29	0–62	Cuijpers et al., 2020
• Adolescents (13–18 years)	28	0.55	0.34; 0.75	79	71–85	453 comparisons
• Young adults (≥18–24 years)	27	0.98	0.79; 1.16	43	9–64	P for difference
• Middle-aged adults (≥24–55 years)	304	0.77	0.67; 0.87	81	79–83	<0.001
• Older adults (≥ 55–75 years)	69	0.66	0.51; 0.82	80	75–84	
• Older old adults (≥ 75 years)	10	0.97	0.42; 1.52	89	81–93	
Setting						
• Primary care	30	0.40	0.29; 0.51	49	15; 66	Cuijpers et al., 2018a
• Outpatients	39	0.78	0.64; 0.93	52	27; 66	Cuijpers et al., 2018a
• Psychiatric inpatients	23	0.40	0.26; 0.54	4	0; 48	Cuijpers et al., 2021d
• Nursing home residents	11	0.43	0.04; 0.82	64	31; 81	Cuijpers et al., 2021d
Other specific target groups						
• College students	15	0.89	0.66; 1.11	57	23; 72	Cuijpers et al., 2016c
• General medical disorders	75	0.65	0.52; 0.79	80	76; 84	Miguel et al., 2021
• Women only	62	0.64	0.54; 0.75	70	61; 77	Cuijpers et al., 2018a
• Minorities only	13	0.63	0.36; 0.89	73	48; 83	Cuijpers et al., 2018a
Income level country						
• High	297	0.60	0.55; 0.65	59	54; 64	Cuijpers et al., 2018a
• Upper middle	20	0.92	0.74; 1.11	76	61; 83	
• Low/lower middle	6	0.83	0.44; 1.22	88	76; 93	
Depression subtypes						
• Subthreshold depression (adults)	11	0.61	0.34; 0.88	82	67; 88	Cuijpers et al., 2018a
• Subthreshold depression (youth)	12	0.38	0.14; 0.63	61	28; 79	Cuijpers et al., 2021d
• Postpartum depression	49	0.67	0.45; 0.89	80	75; 85	Cuijpers et al., 2021d
• Chronic depression	7	0.70	0.26; 1.14	75	47; 88	Cuijpers et al., 2018a

psychotherapy sessions and effect size, and this was no longer significant after adjusting for other characteristics of the studies (Table 1). Total contact time and duration were also not significant in meta-regression analyses. There was a strong association between number of sessions per week and outcome. An increase from one to two sessions per week boosted the effect size by $g = 0.45$, while keeping the total number of treatment sessions constant. This meta-analysis is 10 years old, and we are currently working on an update to verify if these findings still hold after including the large number of new trials published since then. The association between frequency and outcome was recently tested in a new RCT, which indeed confirmed the superiority of a higher frequency (Bruijniks et al., 2019).

A recent IPD meta-analysis focused on task sharing psychotherapies, in which non-specialist workers with no formal experience in counseling or therapy are trained to deliver psychological treatments (Karyotaki et al., 2022). Task sharing is a promising strategy for addressing the large gap in treatment for depression in low- and middle-income countries (LMICs). In total 11 RCTs (4145 participants) contributed data and the analyses showed that task-shared psychological interventions were associated with small but significant effects on depression (Hedges' $g = 0.32$; 95 % CI, 0.26 to 0.38). It was also found that psychomotor symptoms were significantly associated with the outcomes of task-shared psychological interventions.

The active components of psychotherapies can be examined in component studies. These trials decompose multicomponent therapies and compare the full therapy with a therapy in which one component is left out (dismantling studies) or in which a component is added to an existing therapy (additive studies). In a meta-analysis of 16 RCTs (22 comparisons), 15 components were examined of which four were examined in more than one comparison (Cuijpers et al., 2019b). The pooled difference between all full treatments and treatments with one component removed was small but significant ($g = 0.21$). However, almost all RCTs were found to be heavily underpowered. Only one study had sufficient statistical power to detect a small effect size and found that adding emotion regulation skills increased the effects of CBT. None of the other studies had enough power to detect an effect size smaller than $g = 0.55$ and only one study had low risk of bias. So, this body of literature is not very informative about active components of psychotherapies.

In another meta-analysis we examined if cognitive restructuring, behavioral activation, and CBT (in which both are combined) resulted in differential effects (Ciharova et al., 2021). Using a network meta-analytic methodology, we included all studies comparing the three treatment components with each other or with waitlist or usual care control. The pooling of the 45 included RCTs showed that all three components were superior to usual care and waitlist, but no significant difference was found between the three components.

Component network meta-analysis is an innovative method to examine effective components of interventions, by estimating the individual efficacies of the various components contained in a network of RCTs. In a recent component network IPD meta-analysis of internet-based CBT for depression, we included 48 trials (11,704 participants) (Furukawa et al., 2021a). CBT in these studies included several components, including cognitive restructuring, behavioral activation, problem-solving, relaxation, psychoeducation, interpersonal skills training, relapse prevention and others. The study found suggestive evidence that behavioral activation might be beneficial, and that relaxation might be harmful to add to multicomponent CBT interventions.

3.5. Characteristics of patients: conventional meta-analyses

We have examined the effects of psychotherapies in several specific target populations. In one large meta-analysis we examined the effects of therapies in different age groups (Table 3; Cuijpers et al., 2020c). We found no significant differences between psychotherapies among adult age groups, including young adults, middle-aged adults, older adults (≥ 55 years), and older old adults (≥ 75 years). However, the effects of psychotherapies in children and adolescents were significantly smaller than in adults.

Psychotherapies have also been examined in different settings, including primary care (Cuijpers et al., 2009b), specialized mental health care, psychiatric inpatients, and nursing homes (Table 3). A subgroup analysis comparing different settings (primary care, specialized care, community recruitment and other settings), did not indicate that the effects significantly vary across settings (Cuijpers et al., 2018a). In another meta-analysis of therapies in institutional settings, we found no significant difference between therapies in psychiatric inpatients and

in nursing homes (Cuijpers et al., 2021d).

Another group of meta-analyses examined the effects of psychotherapies in specific target groups, including college students (Cuijpers et al., 2016c), general medical disorders (Miguel et al., 2021), studies exclusively conducted in women (Cuijpers et al., 2018a) and studies conducted exclusively in minorities (Cuijpers et al., 2018a; see also Ünlü et al., 2014). Significant effects were found in each of these target groups, and a series of subgroup analyses did not indicate significant differences between studies in these target groups and other studies (Cuijpers et al., 2018a).

An increasing number of RCTs, especially since 2010 has been conducted in LMICs. In one meta-analysis, we examined whether the effects of therapies differed across income level of the country and whether they were conducted in Western countries (in Northern America, Europe, or Australia; Table 3; Cuijpers et al., 2018b). We found that studies that were conducted in non-Western countries and in LMICs resulted in significantly larger effect sizes (p's < 0.001), and these findings remained significant after adjustment for other characteristics of the studies in meta-regression analyses. This difference may be an artefact related to the small number of trials with low risk of bias in LMICs or for example because of differences in control conditions, especially usual care. However, it can be concluded that therapies are at least as effective in LMICs as they are in high-income countries.

3.6. Characteristics of patients: IPD meta-analyses

Conventional meta-analyses can only examine patient characteristics as predictor of outcome at the aggregated study level, while the data from individuals can vary significantly across individuals in the study. IPD meta-analyses are therefore much better suited to examine patient characteristics as predictors of outcome. For several comparisons included in our meta-analytic project, we have also collected the primary data from included trials, to be able to examine predictors of outcome. In an IPD meta-analysis of 16 RCTs (1700 patients) comparing CBT with antidepressants, it was found that baseline severity was not a significant predictor of differential outcomes for CBT versus antidepressants (Weitz et al., 2015). Another IPD meta-analysis included 7 trials of CBT versus placebo (509 patients), but also did not find that baseline severity predicted outcome (Furukawa et al., 2018).

In a network analysis of the IPD data of 17 trials comparing CBT with antidepressants, we examined whether the symptoms that improved in both treatments differed from each other, and we found that five symptoms (depressed mood, feelings of guilt, suicidal thoughts, psychic anxiety, and general somatic symptoms) showed larger improvements in antidepressants compared to the CBT condition (Boschloo et al., 2019).

In two IPD meta-analyses and one IPD network meta-analysis (total 39 RCTs, 8107 participants) it was found that baseline severity did predict outcome of guided and unguided internet interventions, with guided iCBT showing larger effects in individuals with more severe baseline depression (Karyotaki et al., 2017, 2018a, 2021). In addition, age, sex, educational level, relationship status, employment status were also important predictors of outcome (for personalized prediction of outcome see: https://cinema.ispm.unibe.ch/shinies/iCBT/). In an IPD meta-analysis of internet-based interventions for subthreshold depression (7 RCTs, 2186 participants), it was found that higher baseline severity and older age were associated with better outcomes (Reins et al., 2021). In an IPD meta-analysis comparing CBT with antidepressants it was found that gender was not a significant predictor of outcome (Cuijpers et al., 2014d).

In an IPD meta-analysis comparing CBASP with antidepressants and combined treatment (3 RCTs, 1036 patients; Furukawa et al., 2018), it was found that baseline depression, anxiety, prior pharmacotherapy, age, and depression subtypes moderated the relative efficacy of the treatments (for a personalized prediction of outcomes cf. https://kokoro.med.kyoto-u.ac.jp/CBASP/prediction/).

In a recent IPD meta-analysis, the impact of childhood trauma on the outcomes of treatments of depression was examined (Kuzminskaite et al., 2022). This meta-analysis included trials from our database, but also trials that were identified through other sources, and it also included trials on pharmacotherapy and combined treatments. The meta-analysis found that patients with childhood trauma were more depressed at the start of treatment than other patients. However, the effects of treatment (psychotherapy and pharmacotherapy) were comparable with no significant difference in those with and without childhood trauma.

3.7. Subtypes of depression

Another series of meta-analyses has focused on specific subtypes of depression (Table 3). Two meta-analyses focused on treatment of subthreshold depression, one in adults (Cuijpers et al., 2014e) and one in adolescents (Cuijpers et al., 2021e). It was found that the effects of therapy in subthreshold depression in adults were significantly smaller than the effects in major depressive disorders ($p < 0.01$). This can be expected because the room for improvement is smaller in subthreshold depression. In adults we did find that therapy significantly reduced the incidence of major depression at 6 months follow-up (RR = 0.61, 95 % CI 0.37–0.99). In adolescents we found that therapy reduced depressive symptoms significantly, but we found no evidence that therapy reduced the incidence of major depression at follow-up (Cuijpers et al., 2021e).

In a meta-analysis of psychotherapies in perinatal depression we found moderate to large effects on depression (Table 3; Cuijpers et al., 2023), but also significant effects on social support, anxiety, functional limitations, parental stress, and marital stress. In a previous meta-analysis, it was found that trials in perinatal depression resulted in somewhat smaller effect sizes than studies in other target groups, but that was no longer significant after adjusting for other study characteristics in a meta-regression analysis (Cuijpers et al., 2018a).

Only a relatively small number of trials have compared psychotherapies for chronic depression to control conditions (Table 3; Cuijpers et al., 2010, 2018a). A meta-analysis of these studies did indicate small, but significant effects, although this should be considered with caution because of the small number of trials and their low quality. In a large network meta-analysis comparing psychotherapy with pharmacotherapy and combined treatment (Cuijpers et al., 2020d), it was found that combined treatment was more effective than either psychotherapy or pharmacotherapy alone in patients with chronic or treatment-resistant depression. No significant difference was found between psychotherapy and pharmacotherapy, but that may be related to the small number of trials.

Several methods were used to establish whether participants had a depression. In many studies patients had to meet criteria for a depressive disorder according to a clinical interview, while in many other studies participants had to have a score above a cut-off of a self-report measure. We found no significant difference between the effects of these two types of inclusion criteria (Cuijpers et al., 2018a).

In an IPD meta-analysis comparing CBT with antidepressants (4 studies, 805 patients), we found no indication that CBT or antidepressants was significantly more effective in melancholic or atypical depression, predict outcome independent of treatment group (i.e., a main effect), or predict outcome within a given modality (Cuijpers et al., 2016d). The outcome differences between patients with melancholia or atypical depression versus those without were consistently very small (all effect sizes $g < 0.10$).

3.8. Psychotherapy compared with antidepressants and combined treatments

Building on a series of conventional pairwise meta-analyses (Cuijpers et al., 2013d, 2014f), we conducted a large network meta-analysis of 101 RCTs (11,910 patients) comparing psychotherapies, pharmacotherapies, and combined treatments in adults with depression (Cuijpers

et al., 2020d). Depression in most studies was moderate to severe. Response (50 % improvement between baseline and endpoint) was the main outcome. It was found that combined treatment was more effective than psychotherapy alone (RR = 1.27; 95 % CI: 1.14–1.39) and pharmacotherapy alone (RR = 1.25; 95 % CI: 1.14–1.37) in achieving response at the end of treatment, which was in line with previous meta-analyses. We found no significant difference between psychotherapy alone and pharmacotherapy alone at post-test (RR = 0.99; 95 % CI: 0.92–1.08). Similar results were found for remission. It was also found that study drop-out was significantly lower in combined treatment and psychotherapy alone, compared to pharmacotherapy alone. Comparable results were found for remission and the effect size as outcome, and in a series of sensitivity analyses (including analyses with only studies with low risk of bias, in chronic and treatment-resistant depression, and in studies with severe depression). At 6 to 12 months follow-up combined treatment was more effective than pharmacotherapy and psychotherapy alone, but psychotherapy was also significantly more effective than pharmacotherapy. In a separate IPD meta-analysis of 7 RCTs comparing the combination of psychodynamic therapy plus antidepressants (482 adult participants) with antidepressants alone, it was also found that combined treatment was more effective, also at follow-up (Driessen et al., 2020).

We also conducted a network meta-analysis of psychotherapy, pharmacotherapy, combined treatment, usual care, and waitlist in adult depression in primary care (58 RCTs; Cuijpers et al., 2021f). Both psychotherapy and pharmacotherapy were significantly more effective than care as usual and waitlist, but again we found no significant differences between the two. Combined treatment was also more effective than psychotherapy but did not reach significance levels when compared with pharmacotherapy.

Some trials comparing psychotherapy with pharmacotherapy also include a placebo pill condition, so that patients in the pharmacotherapy group are masked for the condition to which they are assigned. This may not be a completely fair comparison, because psychotherapy is never masked, as patients know that they are in the therapy condition. Patients in the therapy conditions may therefore have expectations of positive effects and hope that the therapy will work. In one meta-analysis we therefore examined studies comparing psychotherapy with pharmacotherapy for adult depression in which a placebo was used separately from those in which no placebo was used (Cuijpers et al., 2015b). In the studies in which no placebo was used (and patients in both conditions were not blinded), it was found that pharmacotherapy was a little more effective than psychotherapy (g = 0.13) and this was significant. However, many medication trials are sponsored by the industry, and this may also affect outcomes. In a meta-analysis in which we explored the influence of sponsorship on the outcomes of these trials, we found that in the industry-funded trials pharmacotherapy was significantly more effective than psychotherapy in adult depression (g = 0.11; Cristea et al., 2017). In the trials that were not funded, no significant difference between the two treatments was found (g = 0.10 in favor of psychotherapy). It seems safe to conclude that factors like this can have a small influence on the differential effects of psychotherapy and pharmacotherapy, but overall, the comparable effects seem robust, as was also found in the large network meta-analysis comparing psychotherapy, pharmacotherapy, and combined treatment.

In an important network meta-analysis on the longer-term effects of treatments of adult depression, trials were included that examined an initial acute-phase treatment, but also the maintenance phase up to on average one year (81 RCTs, 13,722 participants; Furukawa et al., 2021b). This meta-analysis included trials from our database, but also trials that were identified through other sources, and it also included trials on pharmacotherapy, combined treatments, and relapse prevention. Patients could be randomized in the acute phase to psychotherapy, pharmacotherapy, combined treatment, standard treatment in primary or secondary care, or pill placebo. In the maintenance phase they could continue the treatment, or switch to another treatment. The main outcome was sustained response, defined as responding to the acute treatment and subsequently having no depressive relapse through the maintenance phase. Psychotherapy kept the patients well significantly more often than pharmacotherapy, both when these treatments were continued into the maintenance phase and when they were followed by discretionary treatment. Combined treatment was the most effective in terms of sustained response. Standard treatment in primary or secondary care had an average sustained response rate of 29 %, while psychotherapy or combined treatment resulted in 12 to 16 % higher response rates.

3.9. Negative effects

Unfortunately, very little research has focused on possible negative effects of psychotherapy, and it has been assumed for a long time that negative effects are not very relevant in psychotherapy, because “it is only talking” (Cuijpers, 2021). In one meta-analysis we checked all RCTs from our database on psychotherapy versus control, to verify whether they reported deterioration rates (Cuijpers et al., 2018c). We included 18 RCTs (23 comparisons), most of which examined clinically significant deterioration according to the definition of Jacobson and Truax (1992). We found that the median risk for deterioration was 4 % in the therapy conditions and 11 % in the control conditions, with a relative risk of RR = 0.39 (95 % CI: 0.27 ~ 0.57).

We already discussed a meta-analysis we conducted to examine the absolute response and remission rates in psychotherapy and control condition (Cuijpers et al., 2021b). In this meta-analysis we also estimated the clinically significant deterioration rates and found a pooled deterioration rate of 5 % in psychotherapy, 12 % in care-as-usual and 13 % in waitlist control groups (RR of therapy versus usual care: 0.37; 95 % CI: 0.29–0.48; NNH = 4.9).

In IPD meta-analyses, deterioration rates can be examined directly in the primary data of RCTs. While individual RCTs typically do not have the statistical power to examine rare outcomes, such as deterioration rates, IPD meta-analyses can allow to generate sufficient power. In one IPD meta-analysis of RCTs comparing CBT with antidepressants in adults depression (16 trials, 1700 patients; Vittengl et al., 2015) it was found that 5 to 7 % of patients showed any deterioration (an increased score on the 17-item HAM-D-17 or BDI of one point), 1 % showed reliable deterioration (an increase of >8 points on the HAM-D-17 or >9 points on the BDI), and 4 % to 5 % showed extreme non- response (had a post-treatment HAM-D score of 21 or higher or a BDI score of >31). No significant difference between CBT and antidepressants was found on any of these rates. Two other IPD meta-analyses showed that the reliable deterioration rate was 3 % in internet-based CBT for depression with support and 6 % in unguided internet-based CBT, and in both IPD meta-analyses these rates were significantly higher in the control conditions (Ebert et al., 2016; Karyotaki et al., 2018b).

IPD meta-analyses are not only capable to calculate average deterioration rates of interventions, but they also have enough statistical power to examine which participants have an increased risk to deteriorate. In one IPD meta-analysis it was found that the risk for deterioration was higher in guided internet-based CBT for depression among people with lower levels of education (Ebert et al., 2016).

4. Discussion

We presented an overview of a series of meta-analyses published over the past 16 years on a MARD on psychotherapies for depression. This MARD covers all RCTs on psychotherapy for depression, regardless of the comparator, target or age group, or type of therapy. We found that the number of RCTs has increased considerably over time and the database now includes >870 RCTs. The 118 meta-analyses have shown that most research has been conducted on CBT, but several other therapies have also been found to be effective in the treatment of depression. Treatments are effective when delivered in individual, group, telephone,

and guided self-help format. They are less effective when delivered without any kind of human support. Therapies have been found to be effective in many different target groups such as college students, women with postpartum depression, and patients with general medical disorders. They are also effective across different age groups, although the effects are significantly smaller in children and adolescents than in adults. We also saw that the effects of psychotherapies have been overestimated because of the low quality of many trials as well as publication bias. Psychotherapies have comparable effects as pharmacotherapy at the short term but are probably more effective at the longer term. Combined treatment is more effective than either psychotherapy or pharmacotherapy at the short, but also at the longer term.

This paper shows the additional benefit of the MARD as a next step in the aggregation of results from randomized trials. Because of the very large number of trials on psychological treatments of depression, conventional methods to integrate trial results can no longer give an overview of all knowledge from trials on these treatments. Although the time and resources needed to build this MARD were considerable, this paper has shown that there is an enormous body of knowledge on psychological treatments, that is difficult to be summarized and integrated in other ways. Knowledge of type of treatments, comparative outcomes among therapies, comparative effects with pharmacotherapy and combined treatment, effects across age groups, specific target groups, settings, different types of therapy, and many other clinically relevant elements of therapies have all been examined extensively, and our MARD has integrated all this in a comprehensive and methodologically consistent way.

It is difficult to give general recommendations for future research because of the wide variety of meta-analyses included in this review and such recommendations could be given for each published meta-analysis separately. However, several more general recommendations can be made. One general recommendation could be that there is no need for new treatments for depression as the treatments up to now have all been proven to be effective, but none is more effective than others. More therapies seem to have little chance, therefore, to be actually more effective than other therapies. If a new treatment is developed, it should be tested in a comparative, sufficiently powered randomized trial to actually show that it is indeed superior to the other therapies (Cuijpers, 2015). Another general comment is that it may be time now to stop conducting randomized trials comparing therapies with control conditions. It is clear that psychotherapies work in general and more specific groups. More trials will not add much to this knowledge. Maybe it is better to move away from such trials and focus more on other clinical questions that are also relevant (Cuijpers, 2023), for example, in fractional factorial designs to examine effective components or stepped wedged designs to examine implementation in routine care. Other general comments could include recommendations to focus more on long-term effects, effectiveness in minority populations, increasing the number of high-quality trials and a stronger focus on negative effects.

This study has several important limitations to be considered when interpreting the results. First, it is not possible to summarize all the results of the published meta-analyses over the years. Each published meta-analysis contains much more details and additional information than we could summarize in this paper. We were also not able to summarize all published meta-analyses and decided not to describe protocols and papers on methodological issues (which would require a full review paper of its own). Then there are also some subsets of our database that have not (yet) been extracted and published. This is the case for the subset of top-down psychological treatments (Cristea et al., 2021) and a category of "other" RCTs with comparisons that do not fit into one of the other categories. We also did not register the current review because all published meta-analyses were based on the same meta-analytic database, searches and extracted data, and this paper is therefore not a regular review. Furthermore, because the meta-analyses have been published over a period of 16 years, the methodology has improved considerably, and older meta-analyses may not meet current methodological standards. For example, in the current meta-analyses a study protocol is always registered in advance and two researchers extract all data of included studies, but this was not the case for all older meta-analyses. An advantage of a MARD is that all RCTs from a research field are included and analyzed in a consistent way. However, it may very well be possible that other meta-analyses, using other methodologies, would result in different findings. We were not able in this overview to compare our findings with those from other meta-analyses examining comparable research questions. Finally, we included only studies in which participants are currently depressed and have excluded studies aimed at participants who remitted after treatment and then received a relapse prevention or maintenance treatment.

Despite these limitations, we can conclude that psychotherapies play an important role in the treatment of depression and that they can contribute considerably to a reduction of the disease burden of depression. This study also demonstrates that MARDs are an important innovation to gain actionable insights from the ever-growing number of RCTs on the psychological treatment of depression.

CRediT authorship contribution statement

PC and EK had the idea for this paper; PC wrote the first draft; all authors contributed considerably to the data collection, analysis and interpretation of results; all authors critically read the paper and approved the final version.

Declaration of competing interest

None.

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Appendix A. Supplementary data

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