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Research paper

Baseline depression severity as moderator on depression outcomes in psychotherapy and pharmacotherapy

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ABSTRACT

Background: Evidence-based treatments for adult depression include psychotherapy and pharmacotherapy, yet little is known about how baseline depression severity moderates treatment outcome.
Objectives: We aimed to compare the effects of psychotherapy and pharmacotherapy for adult depression and to examine the association between baseline depression severity and treatment outcome, converting multiple baseline depression measures into the scores of the Beck Depression Inventory, second edition (BDI-II).
Methods: We conducted systematic searches in bibliographical databases up to September 2022 to identify randomized controlled trials (RCTs) in which psychotherapy was compared with pharmacotherapy in the treatment of adult depression. Various meta-regressions using the baseline depression severity as predictor of the relative effects of psychotherapy and pharmacotherapy were performed.
Results: We identified 65 RCTs including 7250 participants for the meta-analyses and 56 RCTs including 5548 participants for the meta-regression. We found no significant difference between psychotherapy and pharmacotherapy ($g = -0.08$, 95 % CI: −0.2 to 0.04, $p = 0.193$) and baseline depression severity was not significantly associated with the relative effects of psychotherapy and pharmacotherapy ($B = 0.0032$, SE = 0.0096, $p = 0.74$). Results were similar in several sensitivity analyses.
Limitations: Limitations included the low quality of the included studies, and the omission of long-term effects and within-study variability.
Conclusions: We found no indication for a moderation effect of baseline depression severity on the relative effects of psychotherapy and pharmacotherapy. Thus, other factors such as availability and patients' preference must be considered when deciding for treatment options.

Major depressive disorder (MDD) is a highly prevalent disorder and leading source of disability worldwide. Various evidence-based interventions for depression exist, including psychotherapy and pharmacotherapy (Cuijpers, 2017; Cuijpers et al., 2020a). Different classes of antidepressant medications, such as selective serotonin reuptake inhibitors (SSRIs) or tricyclic antidepressants (TCAs), are effective and have produced comparable results between each other (Cipriani et al., 2018). Similarly, numerous clinical trials have shown the superiority of psychotherapies over control conditions in treating depression with little differences between the major psychotherapeutic types (Barth et al., 2013; Cuijpers et al., 2021b; Palpacuer et al., 2017). Most recent network meta-analytical evidence suggests comparable effectiveness between cognitive behavioral therapy (CBT), behavioral activation therapy (BAT), problem-solving therapy (PST), "third wave" therapies, interpersonal psychotherapy (IPT), psychodynamic therapy and life-review therapy. Only non-directive supportive counseling was found to be less effective than the other therapies (Cuijpers et al., 2021b). Further, when directly comparing psychotherapy and pharmacotherapy, both appear to be comparably effective in the treatment of adult depression (Cuijpers et al., 2020b; however, see Cuijpers et al., 2010 for an advantage of pharmacotherapy in chronic depression).

Importantly, not all patients respond equally well to depression

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treatment (Cuijpers et al., 2021a; Rush et al., 2006). Only about 41 % of depressed individuals respond to their first therapy, while >50 % of those receiving therapy do not respond at all (Cuijpers et al., 2021a). Thus, to ensure optimal response, it remains a key challenge to offer patients the intervention that best fits their individual characteristics (Cohen and DeRubeis, 2018).

One important characteristic that can be considered for treatment choice is depression severity prior to treatment commencement (Zimmerman, 2019). Generally, most treatment guidelines recommend medication as the treatment of choice for severe depression (Zimmerman, 2019). For example, the American Psychiatric Association (2010) as well as the NICE guidelines for depression in adults (National Institute for Health and Care Excellence, 2011) have recommended psychotherapy for milder depression and suggest the use of pharmacotherapy alone or in combination with psychotherapy for more severe depression.

However, these guidelines are not entirely in line with existing evidence. More recent conventional and individual patient data meta-analyses (IPDMAs) indicated no evidence of an association between baseline depression severity and treatment outcome when comparing psychotherapy against pharmacotherapy (CBT vs. Pharmacotherapy, Weitz et al., 2015), combined treatment (Cuijpers et al., 2020b), control conditions (Driessen et al., 2010), or pill-placebo (Furukawa et al., 2017). In contrast, there is even IPDMA evidence suggesting that psychotherapy results in greater effects for individuals with severe depressive symptoms when compared to control conditions (Bower et al., 2013; van Bronswijk et al., 2019; Whiston et al., 2019; for a systematic review, see: Cuijpers et al., 2022a).

The evidence available for pharmacotherapy is similar. Most IPDMAs found no indication for an association between baseline depression severity and treatment outcome when comparing pharmacotherapy with pill placebo (Gibbons et al., 2012; Mosca et al., 2017; Rabinowitz et al., 2016). However, there is also IPD meta-analytic evidence that shows significantly higher effectiveness of pharmacotherapy with increasing baseline severity (Stone et al., 2022). When considering conventional meta-analytic data, pharmacotherapy was found to increase in effectiveness relative to pill placebo with higher baseline severity (Khan et al., 2002; Kirsch et al., 2008; for an overview, see: Zimmerman, 2019).

Little is known about the impact of baseline severity when directly comparing psychotherapy with pharmacotherapy, as few studies have examined this relation (see above). Psychotherapy was mostly compared to control conditions (Bower et al., 2013; Driessen et al., 2010; van Bronswijk et al., 2019; Whiston et al., 2019) or only certain psychotherapies (e.g., CBT; Weitz et al., 2015) were compared to pharmacotherapy, while pharmacotherapy was mostly compared to pill placebo (Gibbons et al., 2012; Khan et al., 2002; Kirsch et al., 2008; Mosca et al., 2017; Rabinowitz et al., 2016; Stone et al., 2022). Yet, the direct comparison of psychotherapy and pharmacotherapy is also important as it has practical implications for treatment guidelines and can assist patients' and therapists' treatment choices.

Moreover, most of the previous studies on baseline severity were IPDMAs. Although having their methodological advantages for moderation testing (Cuijpers et al., 2022a), they have possibly not included all available trials due to the difficulties related to obtaining the individual participants' datasets. Conventional meta-analyses using aggregated data offer the possibility of including all eligible trials in the analyses. It is also possible to test for moderators in conventional meta-analyses using meta-regressions. Meta-regressions are similar to simple regressions, meaning that an outcome variable (the effect size) is predicted by an explanatory variable (study characteristics; The Cochrane Collaboration, n.d.). The last conventional meta-analysis and meta-regression focusing on baseline severity and treatment outcome was conducted in 2020, but did not directly compare psychotherapy and pharmacotherapy in relation to baseline severity (Cuijpers et al., 2020b).

Additionally, all previous meta-analyses on this topic have conducted separate meta-regressions for each depression measure to predict therapy outcome. For example, Driessen et al. (2010) used the baseline depression score measured with the Beck Depression Inventory (BDI-I; Beck et al., 1961), the revised Beck Depression Inventory (2nd ed.; BDI-II; Beck et al., 1996) and the Hamilton Depression Rating Scale (HDRS; Hamilton, 1960, 1967) for outcome prediction in separate analyses, respectively. Similarly, Cuijpers et al. (2020b) only used pre-treatment scores measured with the HDRS for their meta-regression. This has likely reduced the number of trials that could have been included into one meta-regression. More specifically, all trials for which the respective outcome measure was not available could not be integrated, thereby decreasing the statistical power and the representativeness of the sample. Thus, to ensure an analysis that includes as many existing studies as possible, it would be necessary to convert different depression measures into one so that all eligible trials on this topic can be included in the analysis. However, depression measures are heterogeneous with low overlap among many scales (Fried, 2017). Still, such conversions of multiple depression measures into one are possible with established algorithms (Furukawa et al., 2019; Leucht et al., 2018; Wahl et al., 2014). Most of these algorithms use a technique called equipercentile linking (Linn, 1993) to identify those scores on each respective measure that have the same percentile ranks, which allows for a nominal translation from one score to the other and thus a direct comparison between different depression measures.

Given these limitations of previous meta-analyses, we conducted a meta-analysis and meta-regression to assess the impact of baseline depression severity on the relative effects of psychotherapy compared to pharmacotherapy in adult depression. For the meta-regression, we converted multiple depression outcome measures into one to include as many existing studies as possible and adjusted for inclusion cut-off of depression severity. Findings can have important clinical implications, indicating whether treatment choice between psychotherapy and pharmacotherapy needs to consider baseline depression severity of the patient. We hypothesized that 1) there is no significant difference between the effectiveness of psychotherapy and pharmacotherapy in treating adult depression and 2) baseline depression severity will not moderate treatment effectiveness in adult depression.

1. Methods

1.1. Identification and selection of studies

The preregistration for this meta-analysis can be accessed here: doi:10.17605/OSF.IO/XDN79. For the identification of studies, we used an existing database of randomized controlled trials (RCTs) on the psychological treatment of unipolar depression. It was developed through a comprehensive literature search (from 1966 to September 2022) within four major bibliographical databases (PubMed, PsycINFO, EMBASE and the Cochrane Library). Terms (both index terms and text words) indicative of depression and psychotherapy were combined and filters for RCTs applied. Psychotherapy was 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). All records and full texts were screened by two independent researchers and any disagreement was solved through discussion. The database has been described in detail elsewhere (Cuijpers et al., 2022b) and all search strings can be found on the website of the project (https://www.metapsy.org/).

For the current meta-analysis, we included all RCTs that 1) compared the effects of psychotherapy of any type (CBT, BAT, psychodynamic therapy, PST, IPT, "third wave" therapies, non-directive supportive therapies, life review therapy, and other therapies that met our definition of psychotherapy) and format (individual, group, and mixed formats), 2) with antidepressant pharmacotherapy of any type (SSRIs,

serotonin-noradrenaline reuptake inhibitors [SNRIs], TCAs, other antidepressants, and mixed prescriptions), 3) on outpatient adults with unipolar depression based on a diagnosis by a clinical interview or validated cut-off scores on self-report measures. For the meta-regression, we included all RCTs that additionally reported baseline depression severity on a measure that has established conversion algorithms to the BDI-II or to any other measure that can be converted to the BDI-II (Furukawa et al., 2019; Leucht et al., 2018; Wahl et al., 2014). The included measures were the BDI-I, the BDI-II, the HDRS 17-item version, the Montgomery-Åsberg Depression Rating Scale (MADRS; Montgomery and Åsberg, 1979) and the Edinburgh Postnatal Depression Scale (EPDS; Cox et al., 1987). We excluded all studies from the meta-regression for which 1) the depression questionnaire version was unclear or 2) the questionnaire was modified, so that a correct conversion was not ensured. Studies including participants with comorbid mental (including psychosis) and somatic disorders were not excluded.

1.2. Risk of bias

The revised Cochrane risk-of-bias tool for randomized trials (RoB 2; Sterne et al., 2019), which was developed to identify possible sources of bias in RCTs, was used to assess the quality of the included studies in five domains: risk of bias 1) arising from the randomization process, 2) due to deviations from the intended interventions, 3) due to missing outcome data, 4) in the measurement of the outcome, and 5) in the selection of reported results, meaning that studies needed to be preregistered with no deviations from this registration. Each study was rated on each domain as low risk of bias, some concerns or high risk of bias and an overall risk of bias was computed for each study respectively. Then, the risk of bias for each domain was aggregated across all included studies. All ratings were performed by two independent persons. Any disagreements were solved through discussion.

1.3. Data extraction and transformation

The database also includes information on participant characteristics (type of depressive disorder, recruitment method, target group, mean age, percentage of women), information on the psychotherapy (type, format, number of session), the type of medication and the country in which the study was conducted in.

For the purpose of this study, we further extracted all cut-off depression scores used as inclusion criterion when recruiting participants in the trials. Many trials use a certain depression severity cut-off score as an inclusion criterion, which can have a significant impact on baseline and post-treatment severity (Zimmerman, 2019) and should therefore be accounted for. We extracted all inclusion cut-offs that were available on a measure that could be transformed into the BDI-II (see above). If multiple cut-off scores on eligible measures were given, we chose the lowest one. After transformation into the BDI-II for harmonizing purposes, all cut-off scores were also transformed into one of four severity categories (0–13: minimal, 14–19: mild, 20–28: moderate, 29–63: severe) based on established metrices (McDowell, 2006) for descriptive reasons (and the continuous scores were used for the analyses).

We transformed the baseline depression severity and the inclusion cut-off score into the BDI-II based on established conversion algorithms by Furukawa et al. (2019), Leucht et al. (2018) and Wahl et al. (2014). We chose the BDI-II because it is a widely used measure and has clear cut-off scores to categorize depression severity (McDowell, 2006). The conversion table can be found in Table 1.

1.4. Outcome measures

For each comparison between a psychological and a pharmacological treatment, an effect size (Hedges' *g*) indicating the standardized mean difference between the two groups was calculated. We chose Hedges' *g* over Cohen's *d*, because Hedges' *g* adjusts for small sample bias (Cuijpers, 2016; Hedges, 1981). For that, the average post-test score of the psychotherapy group was subtracted from the average post-test score the pharmacotherapy group, and then divided by the pooled standard deviations (SDs) of the two groups. Thus, a positive effect size favored pharmacotherapy, while a negative effect size favored psychotherapy. If means and SDs were not reported, we converted dichotomous outcomes (response, remission) or other statistics (e.g., change scores) into effect sizes using the calculateEffectSizes function in metapsyTools package (version 1.0.9) for RStudio. For change scores, this function uses the Hedges' *g* formula, for binary outcomes, *g* is calculated by transforming the log-odds ratio into standardized mean differences, via Chinn's logistic transformation (Chinn, 2000). Depressive symptoms at post-test were the sole outcome measure for this meta-analysis. When more than one depression measure was used in a study, we pooled these measures within one study before pooling the effect sizes across studies. However, we also performed a sensitivity analysis in which we only included one depression outcome per study. This primary outcome was chosen based on the following hierarchy: we gave priority to the BDI-II,

Table 1
Transformation table.

BDI-II	HDRS-17	BDI-I	MADRS	EPDS
0	0	0		0
1	1	1		
2	2	2		1
3	3	3	3	2
5	4	4	4, 5	4
6	5	5	6	5
7*	5,5*	5,5*	6,5*	6*
8	6	6	7	7
9	7	7	8, 9	8
11	8	8	10	9*
12	9	9	11, 12	10
13	10	10	13	11
14*	10,5*	11	13,5*	11,5*
15	11	12	14	12
16	12	13	15, 16	13
17*	12,5*	14	16,5*	14*
18	13	15	17	15
20	14	16	18	16
21	15	17	19	17
22*	15,5*	18	19,5*	18*
23	16	19	20, 21	
24*	16,5*	20	21,5*	
25	17	21	22	20
26*	17,5*	22	22,5*	
27	18	23	23	21
28,5*	18,5*	24	23,5*	
30	19	25	24, 25	
31*	19,5*	26	25,5*	
32	20	27	26	
34	21	28	27	24
35*	21,5*	29	27,5*	
36	22	30	28	
38	23	31	29, 30	
39*	23,5*	32	30,5*	
40	24	33	31	26
42	25	34	32, 33	
43*	25,5*	35	33,5*	
44	26	36	34	
44,5*	26,5*	37	34,5*	
45	27	38	35	
47	28	39	36	
48*	28,5*	40	36,5*	
49	29	41	37, 38	
50	30	42	39	
51		43		
51,5		44		
52,5		45		
53		46		

* imputed by hand using the median between the two closest available numbers.

then the BDI-I, then the HDRS-17, then the MADRS, and then the EPDS. We chose the BDI-II as the first measure, because it is, as mentioned, a widely used measure with clear clinical interpretability that also measures the level of severity very well. We chose the BDI-I next because of its similarity to the BDI-II. The hierarchy of the remaining measures was based on how often each measure was used in the included trials (the HDRS-17 was used most, the EPDS least often).

1.5. Meta-analyses

1.5.1. Psychotherapy versus pharmacotherapy posttreatment effect size

We performed a pairwise meta-analysis comparing psychotherapy and pharmacotherapy for adult depression using a random-effects pooling model, as considerable heterogeneity was expected between studies. When a study contained two or more arms that were eligible for inclusion (e.g., when one study compared two types of psychotherapy with one pharmacotherapy condition), we considered them as separate comparisons and subdivided the comparisons appropriately to avoid double counting.

To examine homogeneity of effect sizes, we calculated I^2-statistics and its 95 % confidence interval (CI). An I^2 of 25 % was considered low heterogeneity, 50 % moderate and 75 % high heterogeneity (Higgins et al., 2003). We also included prediction intervals (PI), which represent 95 % CI of the predictive distribution of effects in future comparable trials. Publication bias was assessed with Duval and Tweedie's trim and fill procedure, with an Egger's test of the intercept and with visual inspection of the funnel plot.

Moreover, we conducted the following sensitivity analyses: 1) one including only the primary outcome based on our hierarchy described above, 2) one including only the studies at low risk of bias, and 3) one excluding outliers (studies of which the 95 % CI of the effect size does not overlap with the 95 % CI of the pooled effect size).

1.5.2. Simple and multiple meta-regression analyses

We then performed a bivariable meta-regression analysis to examine the association between baseline depression severity and the effect size. We used the pooled baseline depression data from the psychotherapy and the pharmacotherapy group as a predictor. We performed multiple sensitivity analyses: we repeated the analysis 1) including only the studies which have originally used the BDI-II in their baseline assessment to verify our conversion. We then repeated this procedure for each originally used questionnaire, i.e., only the studies which have originally used the 2) BDI-I, 3) the HDRS-17,4) the MADRS and 5) the EPDS. We also conducted a simple meta-regression with the inclusion cut-off as a predictor, to assess the association between inclusion cut-off and effect size.

Next, we performed a multivariable meta-regression analysis with baseline severity as one predictor and several study characteristics as controls. We adjusted for 1) inclusion cut-off, 2) the type of psychological therapy (CBT versus all others), and 3) the type of pharmacotherapy (SSRIs versus all others). To perform the meta-regression analyses, we created two dummy variables for the categorical variables. One indicated the use of CBT with all other psychotherapy types as a reference group. The other indicated the use of SSRIs with all other pharmacotherapy types as a reference group. To check for collinearity between predictors, we calculated correlations between all included variables. If a correlation was >0.6, we excluded one variable from the analysis. We repeated the meta-regression 1) including only one measure per study based on the hierarchy previously described, 2) including only those studies which have been rated as low risk, and 3) excluding outliers as sensitivity analyses.

All analyses were conducted with Rstudio, using the metapsyTools package version 1.0.9, which imports functionalities from *meta* and *metafor* (Balduzzi et al., 2019; Harrer et al., 2022; Viechtbauer, 2010).

2. Results

2.1. Selection and inclusion of studies

The PRISMA flow-chart (Fig. 1) summarizes the study selection and inclusion process. The database includes a total of 857 RCTs on adult depression. Sixty-five of those met our inclusion criteria for the meta-analyses, and 56 for the meta-regression. Detailed reasons for exclusion can be found in the PRISMA flow-chart.

2.2. Characteristics of included studies

The 65 trials included 78 comparisons with 3717 participants in the psychotherapy and 3533 participants in the pharmacotherapy group (total $n = 7250$ participants). The most relevant study characteristics are summarized in Table 2. In brief, CBT ($N = 40/78$, 51 %), followed by IPT ($N = 14/78$, 18 %) were the most commonly used psychotherapies, and SSRIs ($N = 31/78$, 40 %), followed by TCAs ($N = 16/78$, 21 %) the most commonly used pharmacotherapies. The most commonly used psychotherapy format was individual ($N = 62/78$, 81 %). Most studies recruited their participants from a clinical sample ($N = 29/65$, 45 %) and were conducted in the USA ($N = 26/65$, 40 %). Ten studies (15 %) were conducted in low- and middle-income countries. The mean age of participants ranged from 25 to 71 years, with a mean across studies of 40 years (SD = 9), and the percentage of women from 42 % to 100 %, with a mean of 72 %. MDD based on DSM, Research Diagnostic or Feighner criteria was the most used diagnosis for inclusion ($N = 49/65$, 75 %).

In most of the 56 studies included into the meta-regression, participants needed to be at least moderately depressed to be included into the trials ($N = 24/56$, 43 %). Seven studies used an inclusion severity cut-off of 'minimal' (13 %), eight of 'mild' (14 %) and only one of 'severe' (2 %) depressive symptoms. The mean converted BDI-II score at baseline ranged from 17 (mild depression) to 50.5 (severe depression), with a mean across studies of 29.99 (SD = 5.65).

2.3. Risk of bias assessment

The risk of bias across studies was considerable (Fig. 2; McGuinness and Higgins, 2020). A total of 18 (28 %) studies reported an adequate randomization process, 29 (45 %) adequately minimized deviations from the intended interventions, five (8 %) studies had a low risk due to missing outcome data, 49 (75 %) studies adequately measured the outcome, and ten (15 %) studies had registered their trial and did not deviate from this registration. Overall, no study met the criteria to be considered at a low risk of bias, 21 studies were rated as having some concerns, and all others as high risk.

2.4. Meta-analyses

Table 3 summarizes the results of the meta-analysis, including all sensitivity analyses. The primary analysis, in which we pooled multiple measures per arm, resulted in no significant difference between psychotherapy and pharmacotherapy ($g = -0.08$, 95 % CI: −0.2 to 0.04, $p = 0.193$). Heterogeneity was high with an I^2 of 78.09 % (95 % CI: 72.92 to 82.27 %), and the PIs were broad ranging from −0.98 to 0.82, suggesting that future studies will have a wide range of outcomes favoring either psychotherapy or pharmacotherapy. A summary of the outcomes is presented in a forest-plot (Fig. 3). Sensitivity analyses selecting one outcome measure per study and removing 12 arms as outliers yielded comparable results (Table 3). We were not able to perform a sensitivity analysis only including the studies with low risk of bias as no study was rated as such. There was an indication for potential publication bias. Egger's test was significant ($p = 0.0229$), pointing at significant asymmetry of the funnel-plot (Fig. 4). Duval and Tweedie's trim and fill procedure indicated 13 missing arms. Adjustment for these missing arms resulted in an effect size of $g = 0.08$ (95 % CI: −0.07 to 0.23, $p = 0.29$),

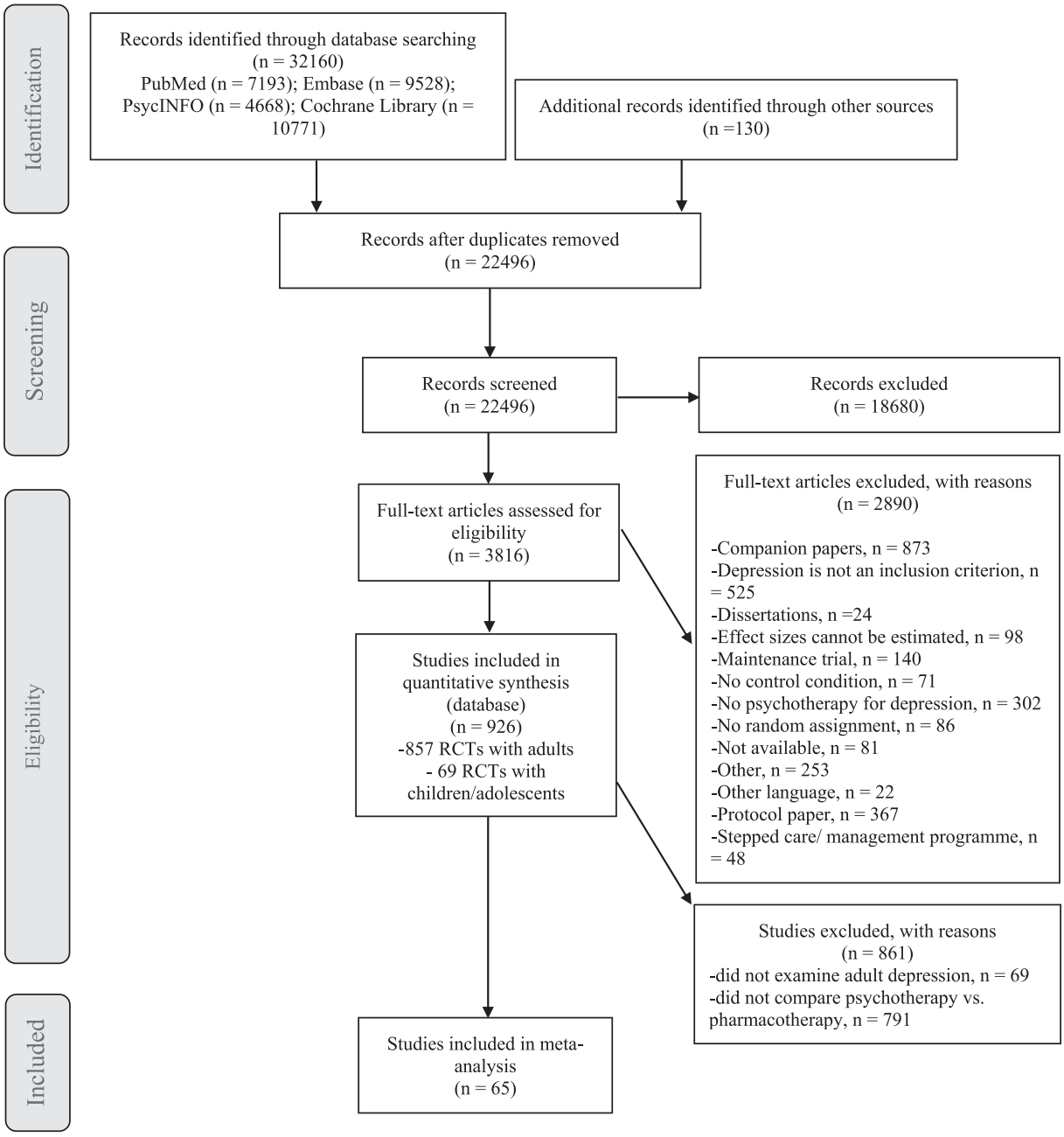

Fig. 1. PRISMA flowchart of study inclusion.

showing no evidence of a difference between psychotherapy and pharmacotherapy.

2.5. Meta-regression

The results of the simple meta-regressions are summarized in Table 4. Mean depression baseline severity did not significantly predict the effect size ($k = 67$; $B = 0.0032$, SE $= 0.0096$, $p = 0.74$), indicating no evidence of an association between baseline depression severity and the relative effects of psychotherapy versus pharmacotherapy. This was also confirmed with a sensitivity analysis including only those studies which have originally used the BDI-II for their baseline assessment ($k = 8$; $B = 0.0324$, SE $= 0.0462$, $p = 0.51$) as well as with sensitivity analyses for all other originally used questionnaires. We did not perform a sensitivity analysis including only those studies which have originally used the EPDS, as only three studies have done so. Further, we did not find an association between inclusion cut-off and the relative effects of psychotherapy and pharmacotherapy ($k = 49$; $B = 0.0012$, SE $= 0.0115$, $p = 0.92$).

To further explore the association between baseline severity and the effects of psychotherapy versus pharmacotherapy, we conducted a multiple meta-regression analysis (Table 5). When adjusting for inclusion cut-off, type of psychotherapy (CBT versus all others) and type of pharmacotherapy (SSRIs versus all others), baseline depression severity was again no significant predictor of treatment outcome ($k = 48$; $B = 0.0043$, SE $= 0.0146$, $p = 0.77$). We obtained the same results when repeating the multiple-meta regression with only one measure per study and when excluding outliers. Again, we could not perform a sensitivity-analysis including only studies at low risk of bias, because there were not any.

Table 2
Characteristics of included studies.

Study	Psycho-therapy	Form.	Pharmaco-therapy	Description of pharmacotherapy	Diag.	Inclusion severity	Mean age	Recr.	% -women	Coun.	RoB
Altamura et al., 2017	ipt	ind	ssri	Sertraline or citalopram	mdd		42.29	clin	78	eu	High
Barber et al., 2012	dyn	ind	Mixed	Sertraline, if non-responding: venlafaxine	mdd	Moderate	37.50	com	59	us	High
Barrett et al., 2001	pst	ind	ssri	Paroxetine	mood	Minimal	44.10	clin	84	us	Some concerns
Basirat et al., 2022	cbt	grp	ssri	Sertaline	mdd	–	31.70	oth	100	oth	Some concerns
Bastos et al., 2015	dyn	ind	ssri	Fluoxetine	mood		29.61	clin	62	oth	Some concerns
Bedi et al., 2000	other psy	ind	Mixed	Not standardized	mdd	–	37.27	clin	75	uk	High
Blackburn et al., 1981	cbt	grp	Mixed	Drug of choice, usually amitriptyline or clomipramine	mdd	Mild	43.30	clin	79	uk	High
Blackburn and Moore, 1997	cbt	ind	Mixed	GPs were free to prescribe any antidepressant of their choice or to switch medication during treatment	mdd	Moderate	39.25	clin	64	uk	High
Blom et al., 2007	ipt	ind	Other pha	Nefazodone	mdd	Moderate	39.95	clin	64	eu	Some concerns
Browne et al., 2002	ipt	ind	ssri	Sertraline	mood	–	42.40	com	68	can	Some concerns
Chibanda et al., 2014	pst	grp	tca	Amitriptyline	mdd	Minimal	25	oth	100	oth	High
David et al., 2008	cbt	ind	ssri	Fluoxetine	mdd	Moderate	36.99	com	66	eu	Some concerns
Dekker et al., 2008	dyn	ind	snri	Venlafaxine	mdd	Moderate	–	clin	74	eu	High
DeRubeis et al., 2005	cbt	ind	Mixed	Paroxetine, if not responding: lithium carbonate or desipramine hydrochloride	mdd	–	40	com	59	us	High
Dimidjian et al., 2006	1: cbt 2: bat	ind	ssri	Paroxetine	mdd	Moderate	39	com	66	us	High
Dunlop et al., 2012	cbt	ind	ssri	Escitalopram	mdd	–	41.60	com	57	us	Some concerns
Dunlop et al., 2017	cbt	ind	1: ssri 2: snri	1: Escitalopram 2: Duloxetine	mdd	Moderate	40	com	57	us	Some concerns
Dunn, 1979	cbt	ind	tca	Not standardized	mood	–	–	clin	70	can	High
Dunner et al., 1996	cbt	ind	ssri	Fluoxetine	mood	–	35.71	oth	46	us	High
Elkin et al., 1989	1: cbt 2: ipt	ind	tca	Imipramine	mdd	Moderate	35	clin	70	us	High
Faramarzi et al., 2008	cbt	grp	ssri	Fluoxetine	mdd	Minimal	28.80	oth	100	oth	High
Finkenzeller et al., 2009	ipt	grp	ssri	Sertraline	mdd	Moderate	67.40	oth	50	eu	High
Frank et al., 2011	ipt	ind	ssri	Escitalopram	mdd	–	39.20	clin	72	oth	Some concerns
Gater et al., 2010	other psy	grp	Mixed	GP offered treatment according to a treatment protocol and following NICE guidelines	mdd	–	41.74	com	100	uk	Some concerns
Gilliam et al., 2019	cbt	ind	ssri	Sertraline	mdd	–	39.60	com	55	us	High
Hautzinger et al., 1996	cbt	ind	tca	Amitriptyline	mood	Moderate	38.80	clin	63	eu	High
Hegerl et al., 2010	1: cbt 2: sup	oth	ssri	Sertraline	mood	Minimal	46.40	clin	68	eu	Some concerns
Hollon et al., 1992	cbt	ind	tca	Imipramine hydrochloride	mdd	Moderate	32.60	clin	80	us	High
Husain et al., 2014	cbt	grp	ssri	Fluoxetine	cut	Moderate	31.30	oth	100	oth	Some concerns
Jarrett et al., 1999	cbt	ind	Other pha	Phenelzine	mdd	–	39.60	com	67	us	Some concerns
Keller et al., 2000	other psy	ind	Other pha	Nefazodone	chr	–	43	clin	65	us	High
Kennedy et al., 2007	cbt	ind	snri	Venlafaxine	mdd	Severe	35.63	clin	63	can	High
Maldonado López, 1982	1: cbt 2: other psy	ind	tca	tca and anxiolytics	mood	–	–	clin	–	eu	High
Markowitz et al., 2005	1: ipt 2: sup	ind	ssri	Sertraline	mood	–	42.30	com	63	us	High

(*continued on next page*)

Table 2 (*continued*)

Study	Psycho-therapy	Form.	Pharmaco-therapy	Description of pharmacotherapy	Diag.	Inclusion severity	Mean age	Recr.	% -women	Coun.	RoB
Marshall et al., 2008	1: cbt 2: ipt	ind	Mixed	Antidepressant medication was prescribed at the discretion of their treating psychiatrist	mdd	Minimal	–	com	69	can	High
Martin et al., 2001	ipt	ind	snri	Venlafaxine	mdd	Moderate	38.94	clin	71	uk	High
McGrath et al., 2013	cbt	ind	ssri	Escitalopram	mdd	Moderate	42	com	56	us	High
McKnight et al., 1992	cbt	ind	tca	Amitriptyline or desipramine	mdd	Moderate	37.50	com	100	us	High
McLean and Hakstian, 1979	1: dyn 2: cbt	ind	tca	Amitriptyline	mdd	Moderate	39.20	com	72	can	High
Mehrotra et al., 2019	cbt	ind	ssri	Sertraline	mood	Mild	51	oth	43	us	Some concerns
Menchetti et al., 2014	ipt	ind	ssri	Sertraline or citalopram	mdd	–	44.90	clin	74	eu	Some concerns
Milgrom et al., 2015	cbt	oth	ssri	Sertraline	mood	Mild	30.10	oth	100	au	High
Miranda et al., 2003	cbt	oth	Mixed	Paroxetine, if not responding or tolerating: bupropion	mdd	–	29.30	oth	100	us	High
Mohr et al., 2001	1: cbt 2: sup	1: ind 2: grp	ssri	Sertraline	mdd	Moderate	43.90	com	73	us	High
Moradveisi et al., 2013	bat	ind	ssri	Sertraline	mdd	Mild	31.37	com	85	oth	High
Murphy et al., 1984	cbt	ind	tca	Nortriptyline	mdd	Moderate	33.80	clin	74	us	High
Murphy et al., 1995	cbt	ind	Mixed	Desipramine, but patients who responded were offered an alternative antidepressant medication of the pharmacotherapist's choice	mdd	Minimal	39.40	com	70	us	High
Mynors-Wallis et al., 1995	pst	ind	tca	Amitriptyline	mdd	Mild	37.10	clin	77	uk	High
Mynors-Wallis et al., 2000	pst	ind	ssri	Fluvoxamine or paroxetine	mdd	Mild	35	clin	77	uk	Some concerns
Parker et al., 2013	cbt	ind	Mixed	Broad spectrum of antidepressant treatment	mdd	–	47.23	com	69	au	High
Petrak et al., 2015	cbt	grp	ssri	Sertraline	mdd	–	48.50	oth	62	eu	Some concerns
Quilty et al., 2014	cbt	ind	Mixed	According to Canadian Network for Mood and Anxiety Treatment	mdd	–	33.61	com	53	can	Some concerns
Rush et al., 1977	cbt	ind	tca	Imipramine	mdd	Moderate	35.70	clin	63	us	High
Salminen et al., 2008	dyn	ind	ssri	Fluoxetine	mdd	Moderate	42.41	clin	68	eu	High
Schramm et al., 2015	other psy	ind	ssri	Escitalopram	chr	Moderate	43.63	clin	54	eu	High
Schulberg et al., 1996	ipt	ind	tca	Nortriptyline	mdd	Mild	38.09	oth	83	us	High
Scott and Freeman, 1992	1: cbt 2: other psy	ind	tca	Amitriptyline	mdd	–	31.79	clin	75	uk	High
Shamsaei et al., 2008	cbt	ind	ssri	Citalopram	mdd	–	36	clin	86	oth	High
Sharp et al., 2010	sup	ind	Mixed	ssri as the first-line treatment, tca or snri as the second-line treatment	mdd	Mild	29.30	oth	100	uk	Some concerns
Sloane et al., 1985	ipt	oth	tca	Nortriptyline	mdd	–	64.40	oth	53	us	High
Spelke et al., 2022	ipt	oth	ssri	Sertraline	cut	Minimal	29.70	oth	100	oth	Some concerns
Thompson et al., 2001	cbt	ind	tca	Desipramine	mdd	Moderate	66.80	com	67	us	High
Weissman et al., 1979	ipt	ind	tca	Amitriptyline	mdd	–	–	clin	–	us	High
Williams et al., 2000	pst	ind	ssri	Paroxetine	mood	Minimal	71	oth	42	us	Some concerns
Zu et al., 2014	cbt	ind	ssri	Citalopram or escitalopram or paroxetine or sertraline	mdd	Moderate	38.54	clin	51	eas	High

Note: Studies in bold font were included in the meta-regression, Form. – format, Diag. – diagnosis, Recr. – recruitment, Coun. – country; *psychotherapy:* bat – behavioral activation therapy, cbt – cognitive behavioral therapy, dyn – psychodynamic therapy, ipt – interpersonal psychotherapy, other psy – other psychotherapies, pst – problem solving therapy, sup – non-directive supportive therapy; *format:* grp – group, ind – individual, oth – other; *pharmacotherapy:* mixed – mixed prescriptions, other pha – other pharmacotherapy, snri – serotonin-noradrenaline reuptake inhibitor, ssri – selective serotonin reuptake inhibitor, tca – tricyclic antidepressant; *diagnosis:* chr – chronic or treatment-resistant depression according to any definition given by the authors, cut – cut-off score (participants score above a cut-off score on a self-rating depression questionnaire), mdd – major depression according to DSM-V criteria, DSM-IV criteria, DSM-III-R criteria, DSM-III criteria, Research Diagnostic Criteria (RDC) for major depression, of Feighner criteria for depressive disorder, mood – mood disorder, e.g., dysthymia; depression NOS; minor depression according

to Research Diagnostic Criteria; *recruitment:* clin – clinical, com – community, oth – other; *country:* au – Australia and New Zealand, can – Canada, eas – East Asia, eu – Europe, oth – other country, uk – UK, usa – USA, numbers indicate different trial arms.

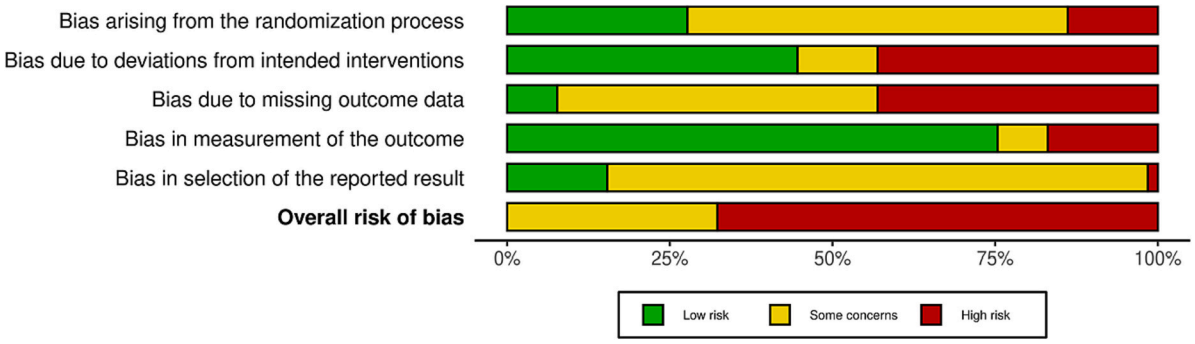

Fig. 2. Risk of bias assessment.

Table 3
Summary of the meta-analyses results.

	k	*g*	CI	*p*	I^2	CI	PI	NNT
All comparisons	77	−0.08	[−0.2; 0.04]	0.193	78.09	[72.92; 82.27]	[−0.98; 0.82]	43.06
Only primary outcomes	77	−0.08	[−0.2; 0.04]	0.206	77.62	[72.3; 81.91]	[−0.99; 0.83]	43.31
Outliers removed[a]	65	0.01	[−0.06; 0.08]	0.756	32.87	[8.69; 50.65]	[−0.25; 0.27]	347.33

Note: k – number of comparisons, NNT – number-needed-to-treat; [a]removed comparisons: Bastos et al., 2015; Dunn, 1979; Faramarzi et al., 2008; Hegerl et al., 2010 (sup); Maldonado López, 1982 (cbt); Maldonado López, 1982 (other psy); Markowitz et al., 2005 (ipt); Markowitz et al., 2005 (sup); Marshall et al., 2008 (ipt); Mehrotra et al., 2019; Murphy et al., 1995; Rush et al., 1977.

3. Discussion

In this meta-analysis and meta-regression, we compared the effects of psychotherapy and pharmacotherapy on adult depression and examined whether baseline depression severity moderated treatment effectiveness. To our knowledge, this is the first meta-analysis examining baseline depression severity as moderator of the relative effectiveness between psychotherapy and pharmacotherapy across the majority of existing studies on this topic. In line with our first hypothesis, we did not find a significant difference between the effectiveness of psychotherapy and pharmacotherapy in the treatment of adult depression. This result was confirmed in two sensitivity analyses, one including only one depression outcome, and one excluding outliers. Again, in line with our second hypothesis, baseline depression severity did not moderate treatment outcome, indicating no difference in the effectiveness of psychotherapy and pharmacotherapy across different baseline severities. This also remained the case when performing sensitivity analyses (including the studies which have originally used the BDI-II in their baseline assessment, the studies which have originally used the BDI-I in their baseline assessment, the studies which have originally used the HDRS-17 in their baseline assessment, the studies which have originally used the MADRS in their baseline assessment, only using one outcome per study for effect size calculation and excluding outliers) and when adjusting for different study characteristics, including the inclusion cut-off.

The finding that there is no significant difference between psychotherapy and pharmacotherapy is supported by previous meta-analytic literature. Recent evidence suggests that both psychotherapy and pharmacotherapy are effective in treating adult depression (Cuijpers, 2017; Cuijpers et al., 2020a). Furthermore, the effects of psychotherapy and pharmacotherapy do not significantly differ when compared in a head-to-head fashion (Cuijpers et al., 2020b). Overall, our analysis confirmed the existing evidence on the relative effectiveness of psychotherapy versus pharmacotherapy. However, it should be noted that the included studies had low quality and possible publication bias. Nevertheless, the current findings support the general notion in the field that both psychotherapy and pharmacotherapy are effective treatments for adult depression.

The finding that there seems to be no significant difference in the effectiveness of pharmacotherapy and psychotherapy across baseline severities has also been reported in previous meta-analyses (Weitz et al., 2015). Weitz et al. (2015) conducted an IPDMA to examine baseline severity as a moderator between the effects of CBT and pharmacotherapy in adult depression. Across 16 trials ($n = 1700$ participants), the authors found that baseline severity was not significantly associated with the treatments' effects. Our study confirmed these findings while examining a much bigger sample of studies ($n = 56$ trials with 5548 participants for the meta-regression) and a wider range of psychotherapies next to CBT (e.g., IPT, PST). It is noteworthy that contradicting results, in which greater effects of psychotherapy (e.g., Bower et al., 2013; van Bronswijk et al., 2019) and pharmacotherapy (e.g., Khan et al., 2002; Kirsch et al., 2008) for individuals with higher depression baseline severity were suggested, were based on comparisons with control conditions, where such findings might be more expected. Therefore, the present findings increase the generalizability of the existing results on the moderating effects of baseline severity in the comparison between psychotherapy and pharmacotherapy.

3.1. Strengths

The present study has several strengths. Firstly, we converted multiple depression measures into one. The reliability of our transformation was supported through a sensitivity analysis including only the studies that originally used the BDI-II as well as sensitivity analyses including only the studies which originally used each converted questionnaire, yielding very similar results. Through the conversion, we were able to include multiple measures that are widely used in research and clinical practice. This increased the diversity through which depression was assessed, possibly reducing the problems that have been reported with single outcome measures such as reliance on physical symptoms (e.g., for the BDI-II: Smarr and Keefer, 2011, for the HDRS: Kriston and von Wolff, 2011). Further, this gave us the opportunity to include more

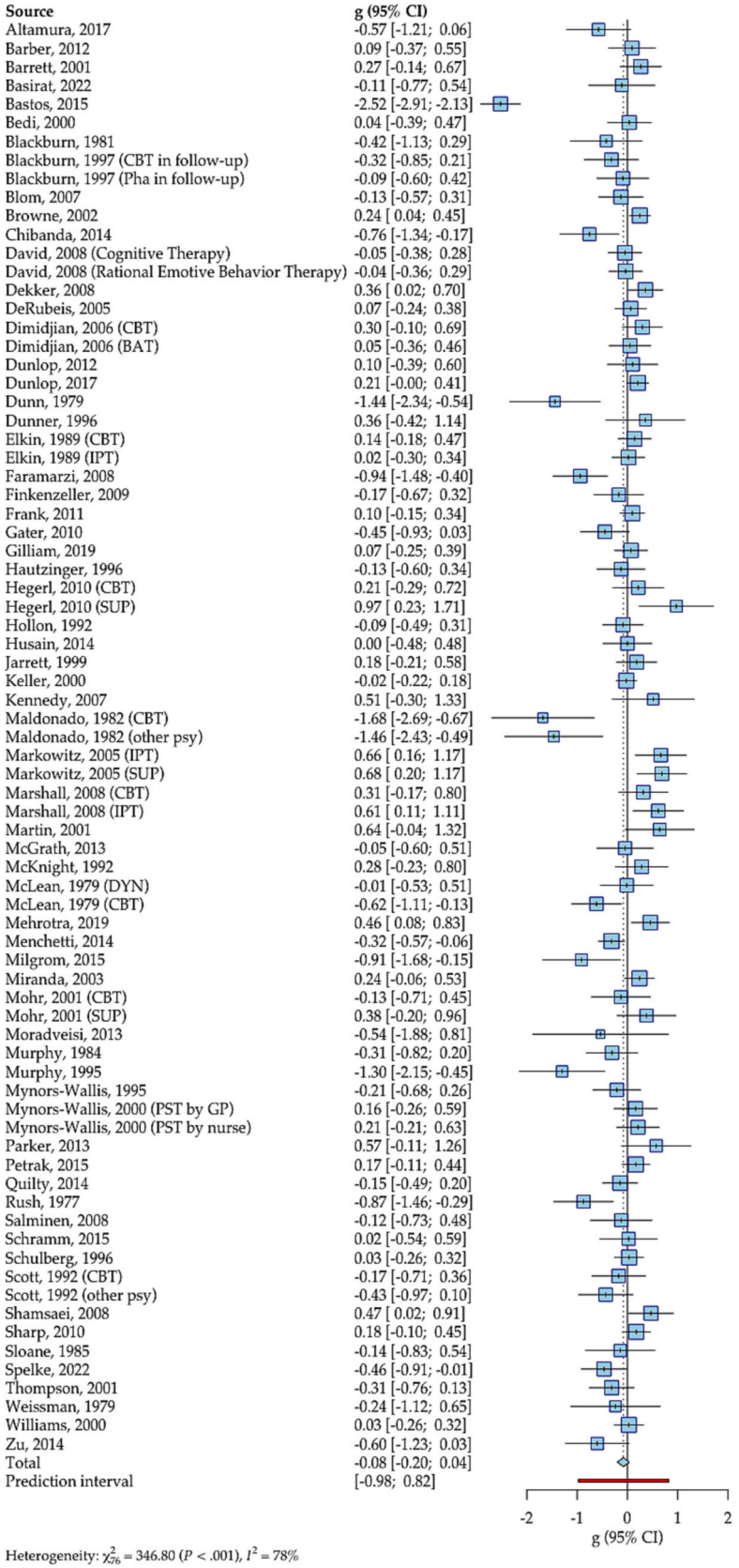

Fig. 3. Forest plot of the main analysis.

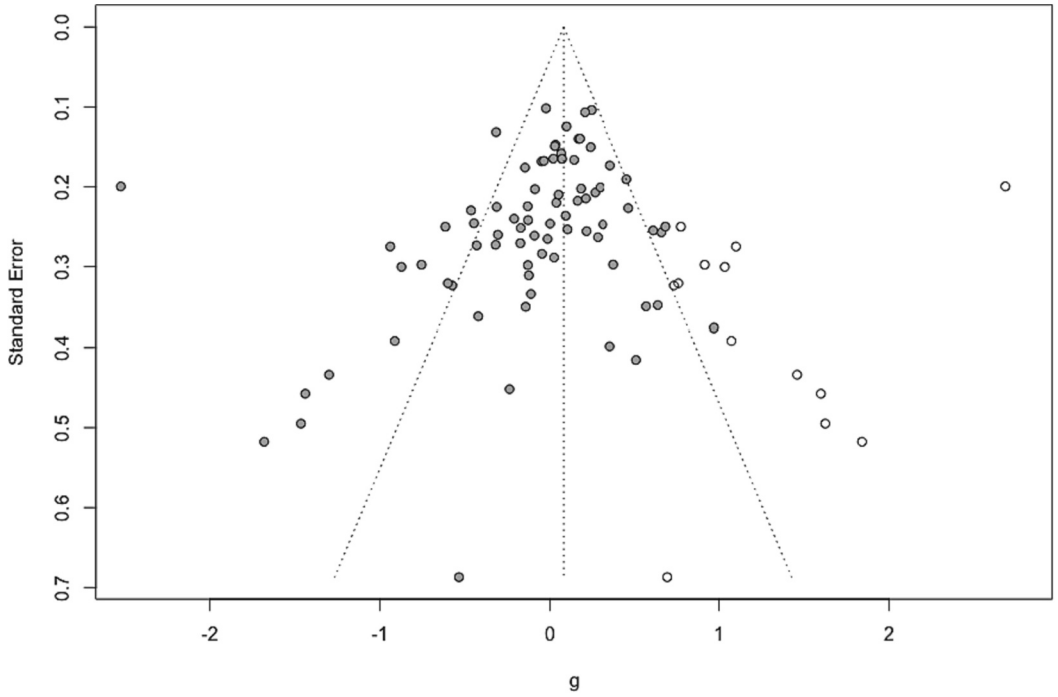

Fig. 4. Funnel plot.

Table 4
Results of the simple meta-regressions.

Included studies	*k*	Variable	B	*SE*	*p*-value
All studies	67	Baseline severity	0.0032	0.0096	0.7407
Original BDI-2	8	Baseline severity	0.0324	0.0462	0.5099
Original BDI-1	32	Baseline severity	0.0079	0.0183	0.6686
Original HDRS-17	42	Baseline severity	−0.0046	0.010	0.6498
Original MADRS	4	Baseline severity	−0.0425	0.0317	0.3121
All studies	49	Inclusion cut-off	0.0012	0.0115	0.9169

Note: *k* – number of comparisons.

Table 5
Results of the multiple meta-regressions.

Included studies	*k*	Variable	B	*SE*	*p*-value
All studies	48	Baseline severity	0.0043	0.0146	0.7700
		Inclusion cut-off	0.0110	0.0157	0.4887
		CBT vs. all others	−0.2145	0.1137	0.0660
		SSRIs vs. all others	0.0631	0.1140	0.5831
Only primary outcomes	48	Baseline severity	−0.0030	0.0144	0.8385
		Inclusion cut-off	0.0157	0.0153	0.3111
		CBT vs. all others	−0.2013	0.1205	0.1020
		SSRIs vs. all others	0.0466	0.1220	07041
Outliers removed	43	Baseline severity	0.0014	0.0110	0.8978
		Inclusion cut-off	0.0110	0.0130	0.4051
		CBT vs. all others	−0.1258	0.957	0.1965
		SSRIs vs. all others	0.0374	0.0928	0.6888

Note: *k* – number of comparisons.

studies into our meta-regression. Secondly, we were the first to adjust for inclusion cut-off, which was important as it can have a significant impact on baseline and posttreatment severity. Thirdly, performing a conventional meta-analysis instead of an IPDMA ensured that we could include more available data, thereby reducing possible availability bias.

3.2. Limitations

However, there are also some limitations to consider. Firstly, the quality of the included studies was rather low. No study was rated as low risk of bias, thus, we were unable to perform sensitivity analyses focusing only on low risk of bias studies. Therefore, the current results must be interpreted with caution. Secondly, it is possible that some nuances of depression scores were lost through the conversion of different depression measures into the BDI-II. However, our conversions were based on established transformation algorithms (Furukawa et al., 2019; Leucht et al., 2018; Wahl et al., 2014) and we obtained the same results when we only analyzed the studies that were not converted. Thirdly, inherent to our methodology, we considered baseline depression severity at the study mean level and ignored potential within-study variability. This may cause a so-called aggregation bias, meaning that the association between baseline depression severity and treatment effect on a group-level may be an under- or overestimation of the true association on a patient-level (Geissbühler et al., 2021). Most of our included studies reported a mean score indicating moderate to severe depression at baseline. However, participants within a trial could still vary in their baseline severity, which we were unable to account for. Fourthly, our depression scale transformations were applied to study-level averages rather than personal scores. Thus, nonlinearities in these transformations may have biased the transformed study-level average. Fifthly, we did not test the null hypothesis of difference, even though we hypothesized to find no difference. Such tests would require methodology different from traditional *p*-values, and our p-values should thus be considered with caution. However, such tests also typically require larger samples, which is why we were unable to perform them. Sixthly, we did not consider long-term effects, even though psychotherapy has been found to have more enduring effects than pharmacotherapy (Furukawa et al., 2021). Lastly, our results are not

generalizable to other patient groups, such as inpatients, children and adolescents, or to patients with comorbid mental disorders. Even though we did not exclude studies that focused on patients with other comorbid mental disorders, we only identified one (Spelke et al., 2022).

3.3. Future research

Several suggestions for future research can be drawn from our study. On a meta-analytic level, it would be important to repeat this work using individual patient data. This would allow to account for individual patient differences in treatment response. Furthermore, previous research has reported superiority of combined treatment versus psychotherapy and pharmacotherapy alone for moderate and possibly severe cases (Cuijpers et al., 2020b). Thus, future studies should perform an (IPD) network meta-analysis and include combined treatment arms. Moreover, treatment personalization and moderators can be further explored using statistical algorithms. On a trial level, future studies should aim to conform more with the criteria for quality assessment to ensure unbiased results. Additionally, they should aim to include a broader spectrum of depression severity, so that conclusions for the least and most severely depressed patients can be drawn as well. Lastly, it is important to acknowledge that pharmacotherapy is more widely accessible than psychotherapy throughout the world and particularly in low-resource settings (Rathod et al., 2017). Thus, future trials should compare pharmacotherapy to psychotherapies that are easier accessible, such as e-health or task-sharing interventions.

3.4. Implications

Our results indicate important implications for clinical practice. Firstly, given that both psychotherapy and pharmacotherapy seem to be equally effective in the treatment of adult depression when considering baseline severity, other treatment and participant characteristics need to be taken into account to optimize treatment effectiveness. For example, psychotherapy has been suggested to be more acceptable and to have more enduring long-term effects than pharmacotherapy (Cuijpers et al., 2020b; Furukawa et al., 2021). Next, many patients with depression prefer psychotherapy (McHugh et al., 2013) over pharmacotherapy, which in turn may influence treatment outcome (Swift et al., 2018). Secondly, as we are not the first to report that baseline severity does not seem to have an influence on treatment outcomes, this finding should be considered in treatment guidelines. As of now, there is no indication why recommendations for pharmacotherapy for more severe cases should be made. Guidelines should instead consider other factors in their recommendations such as patients' preference.

4. Conclusion

In conclusion, we found no indication that baseline depression severity moderates the effects of psychotherapy against pharmacotherapy. Psychotherapy and pharmacotherapy seem to perform equally well, no matter how severe the depression might be. More high-quality studies are needed to further examine long term outcomes and combined treatment options to draw firm conclusions on the moderating effects of baseline severity on treatment outcomes.

CRediT authorship contribution statement

A.T. extracted the data, performed the analyses, done Risk of Bias assessment, and wrote the manuscript. C.M. closely assisted and advised throughout the process and done Risk of Bias assessment. M.C., N.D.P. and G.D. done Risk of Bias assessment. P.C. had the research idea, had an advisory role and assisted with several drafts of the manuscript. E.K. was the senior supervisor and assisted with every step throughout the process. All authors contributed to and have approved the final manuscript.

Declaration of competing interest

None.

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