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Psychological Intervention in Patients with Subthreshold Depression

Individual Participant Data Meta-Analysis of Treatment Outcomes and Effect Heterogeneity

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Key Points

Question. What are the short- and long-term effects of psychological intervention in individuals with subclinical depression, and who benefits most from them?

Findings. In this individual participant data meta-analysis, psychological interventions showed positive effects on symptom reduction, treatment response and deterioration rates. Benefits were found at least up to one year. Individualized treatment benefits varied considerably between patients. Initial depression and anxiety severity were the most credible predictors of differential effects.

Meaning. Psychological interventions should be provided routinely in individuals with subthreshold depression, at least when individuals already experience moderate symptoms (PHQ-9≥10). For very mild symptoms, intervention benefits should be weighed against available resources and potential risks of intervening.

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Supplementary Materials
osf.io/sdqgv

Web Application
metapsy.dev/prevdep-explorer

Abstract

Background. Psychological intervention can be helpful to address depressive symptoms in patients who do not yet meet diagnostic criteria for major depression. Yet, it remains unclear which patients profit most from such treatments, and what long-term effects they have on symptom deterioration, reliable improvement, and achieving close-to-symptom free status.

Aim. This individual participant data (IPD) meta-analysis synthesizes the effect of psychological interventions for subthreshold depression (sD) from post-test up to two years. We also estimate the variability of treatment benefits across patients, and explore effect modifiers.

Results. IPD of 10,671 patients from 50 trials could be included (intervention: n=5,470; control: n=5,201). We found significant effects on depressive symptom severity post-treatment (SMD=−0.48), up to 6 months (SMD=−0.28), and

up to 12 months (*SMD*=−0.27); while effects could not be ascertained up to 24 months (*SMD*=−0.18). Similar findings emerged for 50% symptom reduction (*RR*=1.27-2.79), reliable improvement (*RR*=1.38-3.17), reliable deterioration (*RR*=0.67-0.54), and achieving close to symptom-free status (*RR*=1.41-2.80). Individual treatment effects varied substantially across patients (SD_{SMD}=0.17-0.24). For 8.3%-39.8% of participants, benefits were estimated at zero or lower. Among univariate effect modifiers, only initial depression and anxiety severity were found to be highly credible (*P*>0.99). Predicted treatment effects decreased with lower symptom severity, but remained minimally important even among patients with very mild symptoms (*SMD*=0.33 for a PHQ-9 score of 5).

Conclusion. Psychological intervention can reduce the symptom burden in patients with sD up to one year, and has a protective effect on symptom deterioration. Benefits up to two years are less certain. We find strong support for intervention in sD when symptom severity is at least moderate (PHQ-9≥10), although benefits may differ strongly across individuals. For very mild symptoms, scalable treatments or watchful waiting could be an attractive option.

Introduction

Depressive disorders are highly prevalent in the general population[1]. They are associated with numerous negative outcomes for the individual and society, including an increased risk of suicide[2], and with major depressive disorder (MDD) alone accounting for 7.5% of all years lived with disability[3].

Psychotherapy, pharmacotherapy, or a combination of both are common first-line treatments for MDD[4,5], but their public health impact is limited. It has been estimated that only one third of the global disease burden of MDD can be averted, even if every patient were to receive evidence-based treatments under optimal conditions[6].

One way to meet this challenge is to intervene before individuals develop MDD. Individuals with subthreshold depression (sD) may be the most promising target group for such an approach. Symptoms of sD affect roughly 11% of the general population[7]. They are associated with elevated mortality[8], increased healthcare utilization[9], substantial economic costs[10], and adverse effects on quality of life comparable to MDD[11]. Individuals with sD are also three times as likely to develop MDD than healthy controls[7]. This suggests that intervening in this target group could be helpful to reduce the incidence of new MDD cases, and to treat existing symptoms.

Meta-analytic evidence suggests that psychological interventions are effective in sD, yielding small to moderate benefits[12–16], and that they can reduce the incidence of MDD by 19-43%[17,18]. Almost all this evidence is based on aggregate data meta-analyses. We are only aware of two meta-analyses using individual participant data (IPD), both conducted by our group. These previous studies were limited to digital

intervention trials[15], and trials examining MDD incidence[18]. They included 7 and 30 trials, respectively.

A major strength of IPD meta-analyses (IPD-MAs) is that they can examine heterogeneous treatment effects on a patient level[19]. This may be particularly attractive for psychological interventions in sD, where findings on effect modification remain inconclusive[17,20]. Robust moderators identified using IPD-MA could allow to stratify existing care, by prioritizing psychological intervention among sD individuals who are most likely to benefit. Conversely, they could be used to develop better treatments for those at high risk of non-response. Furthermore, IPD-MA allows to analyze rates of treatment response, remission, and symptom deterioration in a consistent way across all studies. Effects on such secondary outcomes remain understudied in sD populations, as are the benefits that treatment might have over several years.

We therefore conducted an IPD-MA of psychological intervention effects in sD, focusing on depressive symptom severity, 50% symptom reduction, reliable improvement, reliable symptom deterioration, and achieving close to symptom-free status. We analyzed both short- and long-term benefits up to two years. Furthermore, we estimated the heterogeneity of treatment effects in this population, and examined participant-level moderators.

Methods

Registration & Protocol

This study has been registered with PROSPERO (CRD42017058585), with further methodological information provided in a published protocol[21]. For the present IPD-MA, we also preregistered a detailed protocol addendum and statistical analysis plans (SAPs; see osf.io/vba7f and osf.io/28xnc). The SAP also documents all planned deviations from the protocol, and their justification. We report this study following the PRISMA-IPD statement[22].

Eligibility Criteria

Eligible studies were randomized trials in which (1) a psychological intervention (see definition in supplement S1) was compared to a control group (waitlist, care as usual, psychoeducational material, placebo) with regards to (2) effects on depressive symptom severity, (3) as measured by a validated patient or clinician-rated instrument, in (4) adults without MDD at baseline, (5) as confirmed by a standardized diagnostic interview.

We also included studies in which participants were eligible regardless of MDD status; but only when the diagnostic status was assessed at baseline, so that baseline MDD cases could be excluded. Individuals were considered to experience sD when displaying at least mild depressive symptom severity at baseline. If trials did not employ inclusion cut-offs, individuals experiencing less than mild symptoms were removed, using a cut-off equivalent to a score of 5 on the Patient Health Questionnaire (PHQ-9)[23,24].

Study Identification

Eligible studies were identified by two independent researchers screening full-texts of the "Metapsy" (metapsy.org) meta-analytic research domain for depression interventions (docs.metapsy.org/databases/depression-psyctr). This database is updated three times a year by a systematic literature search of the PubMed, Embase, PsycINFO, and Cochrane Central Register of Controlled Trials libraries (see supplement S2 for search strings). During each update, two independent researchers screen the titles and abstracts of all articles, and subsequently review full texts of eligible studies. We also screened previous reviews on the prevention of MDD[12–17,25,26] and contacted senior researchers in the depression prevention field regarding other relevant trials. Studies published until January 1st, 2024, were considered.

Data Collection & Harmonization

We contacted corresponding authors of eligible articles to request permission to use their IPD. Authors who responded were asked to provide data on demographic, clinical, outcome and intervention-related characteristics, if assessed. We included variables as putative moderators if they matched a pre-defined list of characteristics predictive of long-term outcomes in depression[21] (see supplement S3).

Depressive symptom severity measures were transformed into a "common metric" to facilitate joint analyses[24] (see supplement S4). Then, harmonized IPD were merged into a single data set following a standardized protocol[27]. Post-intervention assessments were treated as one assessment, and follow-ups were categorized based on their length (up to 6, 12, 24 months). When eligible trials did not provide IPD, we extracted outcome data for an aggregate data (AD) meta-analysis from the published reports, if feasible.

Risk of Bias

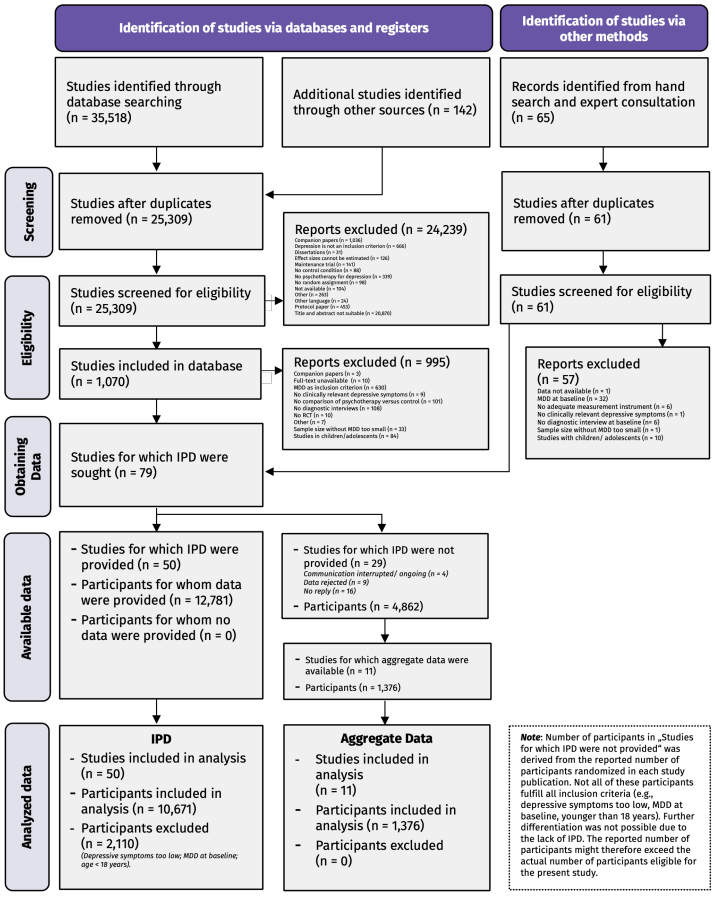
Two independent reviewers assessed risk of bias using Cochrane's RoB-2 tool[28] in each study. We rated all studies as being at low risk of bias for the "missing outcome data" criterion, since multiple imputation with auxiliary variables could be used to handle missing data consistently in this IPD-MA.

Outcomes

The primary outcome of this IPD-MA was depressive symptom severity, as measured by a validated patient or clinician-rated instrument. From the symptom severity scores, we derived the following additional outcomes: (1) 50% symptom reduction compared to baseline (response), (2) close to symptom-free status (remission; defined as scores equivalent to PHQ-9$<$5[23]), as well as (3) reliable improvement and (4) reliable deterioration in depressive symptoms[29].

We focused exclusively on depressive symptom severity, as well as on indicators that can be derived from it. This was done to maximize the number of eligible trials, thus optimizing the statistical power for our examination of treatment-covariate interactions. Among eligible trials, a smaller subset (k=30) also reported MDD onset

Figure 1. *PRISMA-IPD flow chart*.



as confirmed by diagnostic interviews. These preventive outcomes were already examined in a previous study[18].

Statistical Analyses

A detailed description of the statistical analyses is provided in the supplement (S4). All analyses were conducted according to the "intention-to-treat" principle (treatment policy estimand[30]). Multilevel multiple imputation models with heteroscedastic errors were used to impute missing values. Bayesian one-stage IPD-MA models were used to pool effects on all outcomes at post-test and follow-ups. Effects were considered "significant" when the 95% credibility interval (CrI) of the treatment coefficient did not include zero. As a sensitivity analysis, we (1) recalculated all effects using two-stage IPD-MA, (2) conducted a conventional meta-analysis that also included studies which did not provide IPD; (3) calculated effects excluding "bottom-up" therapies[31] and stepped care interventions; and (4) ran analyses adjusting for potential small-study effects and/or selective publication[32–34].

To examine heterogeneous treatment effects across patients, we employed targeted superlearning[49]. Superlearning is an ensemble machine learning approach in which both simple and data-adaptive prediction algorithms are combined. This guarantees that the superlearner will asymptotically perform as well or better than

any individual algorithm included in the framework, and has been shown to perform well even in very small samples[49,50]. Targeted superlearning was used to estimate patient-specific treatment benefits $B(W_k)$ while integrating all available covariate information W_k in a study. The resulting distribution of $B(W_k)$ was used to examine how much individual effects vary within a study, and to estimate how many patients may not benefit from a psychological intervention (i.e., fare similar or worse under treatment than under control)[50]. A detailed description of our approach is provided in the SAP (osf.io/28xnc).

Participant-level moderator analyses were then conducted to examine univariate predictors of differential effects. These analyses were implemented by extending the one-stage IPD-MA models, and focused on symptom severity at the first post-treatment assessment point available in each study. Furthermore, we also examined study-level moderators of the effect. Lastly, we used an additive mixed model[35,36] to examine potentially non-linear interactions between treatment effects and baseline PHQ-9 scores.

Results

Of the 1131 full text articles screened, 79 were eligible for present investigation. IPD could be obtained from *K*=50 (63.29%) of all eligible trials. After enforcing all inclusion criteria, a total of *N*=10,671 individuals (intervention: *n*=5,470; control: *n*=5,201) were included in the IPD-MA. Additional effect size data was available for *k*=11 studies which did not provide IPD (1,376 participants; intervention: 680; control: 696). Figure 1 summarizes the study search and inclusion. Study references can be found in supplement S6.

Study Characteristics

Characteristics of the included studies are provided in supplement S16. The largest proportion of trials were conducted in general adult populations (*k*=14; 28%), followed by older adults (*k*=13; 26%). Cognitive-behavioral therapy (CBT) was the most frequently employed intervention (*k*=24; 48%). Contents were most frequently delivered face-to-face (*k*=22; 44%), followed by the Internet (*k*=15; 30%). Participant-level characteristics (S7) and missing outcome data (S8) are given in the supplement. Most participants (*N*=7,199; 68%) were female. The mean age was *M*=52.79 (SD=18.72). Most studies received a low risk of bias assessment (62%; *k*=31). Eleven (22%) showed high overall risk.

Treatment Effects

Psychological intervention reduced depressive symptom severity significantly at post-test (*SMD*=-0.48, 95%CrI: −0.63 to −0.33; *k*=47), within six months (*SMD*=-0.28, 95%CrI: −0.40 to −0.16; *k*=39), and within one year (*SMD*=-0.27, 95%CrI: −0.37 to −0.16; k=33). No significant effect emerged among studies recording outcomes up to two years (*SMD*=-0.18, 95%CrI: −0.41 to 0.06; k=15). At post-test, our models indicate a >99% posterior probability that treatment effects surpass *SMD*=-0.24. This effect has been determined as a minimally impor-

Table 1. *Pooled effects on depressive symptom severity, response, remission, and deterioration.*

	k	Participants			Effect Size (95% CrI)	NNT§	95%-PI	ŧ (95% CrI)	Relative Risk†	Event Rate†	
		Total	IGs	CGs						Intervention	Control
Depressive Symptom Severity (*SMD*)											
- Post-Test	47	9,418	4,875	4,543	-0.48 [-0.63; -0.33]	6.61	[-1.44; 0.48]	0.47 [0.36; 0.60]	-	-	-
- Up to 6 months	39	8,218	4,152	4,066	-0.28 [-0.40; -0.16]	11.12	[-0.94; 0.38]	0.32 [0.23; 0.43]	-	-	-
- Up to 12 months	33	7,740	3,903	3,837	-0.27 [-0.37; -0.16]	11.52	[-0.77; 0.23]	0.24 [0.16; 0.34]	-	-	-
- Up to 24 months	15	3,163	1,597	1,566	-0.18 [-0.41; 0.06]	15.36	[-1.05; 0.70]	0.39 [0.24; 0.60]	-	-	-
50% Symptom Reduction (*OR*)											
- Post-Test	47	9,418	4,875	4,543	2.79 [1.92; 3.85]	4.83	[0.35; 21.95]	1.01 [0.73; 1.34]	1.82 [1.77; 1.87]	45.8% [44.8%; 47.3%]	25.1% [24.7%; 26.0%]
- Up to 6 months	39	8,218	4,152	4,066	1.92 [1.43; 2.48]	7.25	[0.46; 7.98]	0.69 [0.48; 0.94]	1.45 [1.39; 1.51]	44.2% [42.7%; 45.6%]	30.4% [29.5%; 31.4%]
- Up to 12 months	33	7,740	3,903	3,837	1.92 [1.43; 2.48]	8.40	[0.46; 8.06]	0.69 [0.48; 0.94]	1.36 [1.30; 1.39]	45.7% [44.5%; 46.9%]	33.8% [32.8%; 34.6%]
- Up to 24 months	15	3,163	1,597	1,566	1.27 [0.58; 2.20]	20	[0.13; 12.76]	1.02 [0.57; 1.64]	1.12 [1.07; 1.18]	47% [44.9%; 49.2%]	42% [39.3%; 43.6%]
Close to Symptom-Free Status (*OR*)‡											
- Post-Test	42	8,701	4,512	4,189	2.80 [1.84; 4.00]	5.56	[0.31; 25.23]	1.07 [0.77; 1.43]	1.55 [1.51; 1.59]	50.6% [49.5%; 52.0%]	32.6% [31.8%; 33.3%]
- Up to 6 months	34	7,267	3,674	3,593	1.92 [1.36; 2.59]	8.13	[0.40; 9.36]	0.76 [0.51; 1.07]	1.31 [1.27; 1.35]	50.9% [49.2%; 52.1%]	38.6% [37.9%; 39.7%]
- Up to 12 months	31	7,598	3,833	3,765	1.70 [1.23; 2.25]	10	[0.39; 7.37]	0.70 [0.46; 0.99]	1.23 [1.19; 1.26]	53.4% [52.2%; 54.5%]	43.4% [42.2%; 44.2%]
- Up to 24 months	15	3,163	1,597	1,566	1.41 [0.64; 2.49]	19.61	[0.13; 14.87]	1.04 [0.60; 1.66]	1.10 [1.04; 1.14]	57.5% [55.1%; 59.2%]	52.4% [50.1%; 54.2%]
Reliable Improvement (*OR*)											
- Post-Test	47	9,418	4,875	4,543	3.17 [2.21; 4.36]	6.21	[0.50; 20.04]	0.90 [0.61; 1.24]	1.91 [1.84; 2.01]	34% [32.9%; 35.2%]	17.9% [17.1%; 18.7%]
- Up to 6 months	39	8,218	4,152	4,066	1.92 [1.43; 2.47]	10.87	[0.52; 7.09]	0.63 [0.40; 0.90]	1.44 [1.39; 1.50]	30.5% [29.1%; 32.5%]	21.3% [20.2%; 22.1%]
- Up to 12 months	33	7,740	3,903	3,837	1.88 [1.42; 2.40]	11.36	[0.62; 5.74]	0.53 [0.31; 0.79]	1.41 [1.35; 1.46]	30.3% [29.4%; 31.6%]	21.5% [20.7%; 22.4%]
- Up to 24 months	15	3,163	1,597	1,566	1.38 [0.62; 2.39]	20	[0.14; 13.38]	1.00 [0.54; 1.63]	1.17 [1.11; 1.25]	34.8% [31.4%; 36.5%]	29.8% [25.6%; 31.3%]
Reliable Deterioration (*OR*)											
- Post-Test	47	9,418	4,875	4,543	0.54 [0.35; 0.73]	50	[0.16; 1.75]	0.56 [0.00; 1.06]	0.68 [0.59; 0.79]	4% [3.6%; 4.7%]	6% [5.6%; 6.3%]
- Up to 6 months	39	8,218	4,152	4,066	0.67 [0.47; 0.91]	71.43	[0.26; 1.75]	0.44 [0.00; 0.82]	0.77 [0.64; 0.88]	4.6% [4.2%; 5.4%]	6% [5.6%; 6.4%]
- Up to 12 months	33	7,740	3,903	3,837	0.60 [0.43; 0.79]	47.62	[0.32; 1.10]	0.26 [0.00; 0.69]	0.68 [0.60; 0.77]	4.3% [3.8%; 4.9%]	6.4% [5.9%; 6.9%]
- Up to 24 months	15	3,163	1,597	1,566	0.66 [0.27; 1.23]	250	[0.11; 4.10]	0.77 [0.00; 1.55]	0.92 [0.75; 1.25]	6.1% [4.6%; 8.1%]	6.5% [5.7%; 7.7%]

Note. CGs = control groups; IGs = intervention groups; k=number of studies/effects; OR=odds ratio; PI=prediction interval; SMD=standardized mean difference.

§For effects on depressive symptom severity, NNTs were estimated using the method by Furukawa and Leucht (2011), with control group event rates (CERs) imputed from reliable improvement rates in the CGs; †Calculated using regression standardization (*G*-computation). Marginal risk ratios and their credible intervals may diverge in their interpretation from the conditional ORs measured by the treatment indicator coefficient in the main one-stage IPD-MA model (see "effect size" column). ‡Defined as scoring PHQ-9 < 5. This analysis only included studies which employed the PHQ-9, or some other instrument which could be converted into PHQ-9 scores using the common metric by Wahl et al.[24].

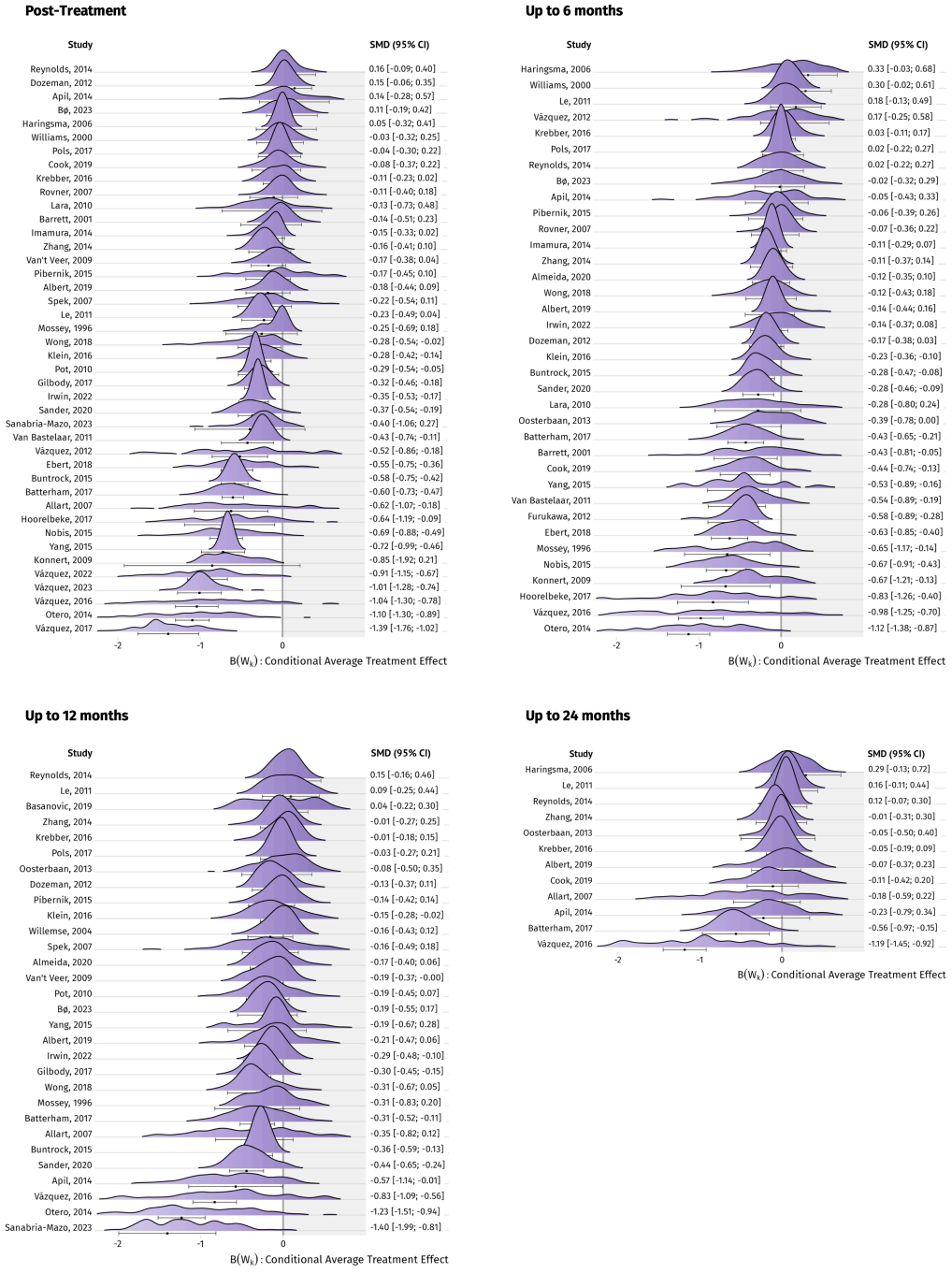
tant threshold that is still relevant from a patient perspective[37]. Up to 6 months, the probability of greater than minimally important effects was 75%; 71.3% up to one year, and 28.9% up to two years.

Similar findings emerged for all other outcomes. From post-test up to twelve months, we found positive effects on 50% symptom reduction, reliable improvement, and achieving close to symptom-free status (*RR*=1.23-1.91). Interventions also had a protective effect on reliable symptom deterioration, reducing the risk between 23%-32%. No significant effects could be ascertained for any of these outcomes up to 24 months. For all favorable outcomes, control group event rates (CERs) increased considerably at later follow-ups. For example, while only 32.6% of control group individuals achieved close to symptom-free status at post-test, this number was 52.4% up to two-years. Table 1 details all one-stage IPD-MA results. Results of sensitivity analyses closely mirrored the main results, and we found no strong indications of publication bias (see supplement S9-S13).

Heterogeneity of Treatment Effects

Figure 2 gives the distribution of patient-specific treatment benefits in each study, as estimated by the targeted superlearner. At all assessment periods, we found that predicted benefits varied considerably between patients. The pooled standard deviation of treatment effects was SD_{SMD}=0.17 at post-test, 0.20 within 6 months,

Figure 2. *Estimated distribution of patient-specific treatment effects*.



Note. Densities show the distribution of conditional average treatment effects $B(W_k)$ ("blips"), as estimated using targeted superlearning. Values of $B(W_k)$ can be interpreted as individualized versions of the causal treatment effect, expressed as SMDs. Squares and whiskers below the densities indicate the average treatment effect (ATE) in each study, and its 95% confidence interval.

0.24 within one year, and 0.23 up to two years. This variability itself differed considerably between studies ($\tau_{\log(\mathrm{SD})}$=0.887-1.170).

Table 2. *Results of participant-level moderator analyses.*

Moderator	*k*	*N*	$\hat{\gamma}$ (95% CrI)	$\hat{\tau}$ (95% CrI)	$P(\|\gamma\|>0)$
Depressive Symptom Severity	50	10,671	-0.09 [-0.14; -0.04]	0.08 [0.01; 0.15]	0.9998
Anxiety Symptom Severity	24	6,229	-0.08 [-0.14; -0.02]	0.05 [0.00; 0.11]	0.9957
Relationship, *yes*	39	8,677	-0.05 [-0.10; 0.00]	0.06 [0.00; 0.11]	0.9717
Previous Psychotherapy, *yes*	10	2,899	0.11 [-0.04; 0.27]	0.07 [0.00; 0.25]	0.9313
Sex, *male*	44	10,588	-0.04 [-0.09; 0.02]	0.08 [0.00; 0.14]	0.9226
Education, *higher*	36	9,577	-0.02 [-0.07; 0.03]	0.06 [0.00; 0.13]	0.7920
Antidepressive Medication, *yes*	17	5,372	0.03 [-0.05; 0.11]	0.08 [0.00; 0.19]	0.7679
Chronic Medical Condition, *yes*	13	4,677	0.02 [-0.07; 0.12]	0.07 [0.00; 0.17]	0.6966
Ethnicity, *non-white*	19	5,370	0.02 [-0.08; 0.13]	0.13 [0.00; 0.24]	0.6529
Employment, *yes*	30	7,786	0.01 [-0.05; 0.06]	0.04 [0.00; 0.11]	0.5929
History of MDD, *yes*	17	3,515	-0.01 [-0.11; 0.08]	0.08 [0.00; 0.20]	0.5904
Age, *years*	49	10,437	-0.00 [-0.06; 0.05]	0.08 [0.00; 0.15]	0.5633

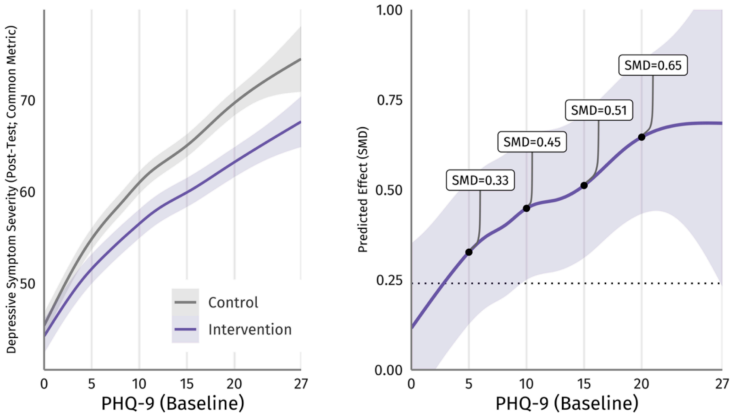
Note. $\hat{\gamma}$=standardized pooled coefficient of the treatment-covariate interaction; *k*=number of studies providing data; *N*=number of participants included in the analysis; $P(|\gamma| > 0)$=posterior tail probability of $\hat{\gamma}$ being greater/less than zero.

At post-test, 8.3% of all patients were estimated to experience identical or worse outcomes under treatment than under control (i.e., SMD < 0). This proportion rose to 16.7% within 6 months, 22.2% within one year, and 39.8% up to two years ($\tau_{\text{logit}(p)}$ =1.572 to 2.251). At metapsy.dev/prevdep-explorer, we present an interactive web application which allows to explore the individualized treatment benefits we estimated in this analysis. This application can also be used to calculate conditional effect estimates for specific patients groups, treatment formats, and comparisons.

Effect Modifiers

Table 2 shows results for participant-level moderators. Only baseline depression and anxiety symptom severity emerged as credible effect modifiers (posterior tail probabilities >99%). For both, higher initial symptom severity predicted

Figure 3. *Symptom severity and predicted treatment effects conditional on PHQ-9 baseline scores*.



Note. treatment groups (*K*=10 basis functions). Models were fitted in the multiply imputed data and predictions obtained using the "predict-then-combine"/pool-last approach. Analyses were restricted to studies including assessments of the PHQ-9 at baseline, or instruments convertible to the PHQ-9 as per the common metric by Wahl et al.[24] (*k*=47, *N*=9,598). Signs of the predicted effect size were reversed, so that SMDs with a positive sign indicate favorable effects of the treatment. A population-level SD of 10 was assumed to standardize the treatment effects, as implied by the common metric[24].

larger effects ($\hat{\gamma}$=-0.09 to −0.08). Probabilities >90% were assigned to three additional variables: relationship status (higher benefits when in a relationship; $\hat{\gamma}$ =-0.05, *P*=0.97), psychotherapy in the past (predicting lower benefits; $\hat{\gamma}$=0.11, *P*=0.93), and sex (higher benefits in males, $\hat{\gamma}$=-0.04, *P*=0.92). Tests of study-level effect modifiers are given in S14. Among study-level variables, only target group was found to be a significant moderator. Lower effects were found in general adult, older adult, chronic pain, and pregnant women populations (*SMD*=-0.18 to −0.41), as well as moderate effects in diabetes patients (*SMD*=-0.60), while the highest benefits emerged in university students (*SMD*=-1.00) and informal caregivers (*SMD*=-1.02). The subgroup-specific effect among studies with low RoB was *SMD*=-0.53 (95%CrI: −0.71 to −0.36).

Figure 3 shows the predicted symptom severity (left) and treatment effect (right) conditional on baseline PHQ-9 values, as estimated by a non-linear interaction model. This analysis largely corroborated the main moderator model, showing that benefits rise with higher initial PHQ-9 values. Predicted treatment effects at established PHQ-9 cut-offs[23] were *SMD*=0.33 (PHQ-9=5; lower cut-off for sD), *SMD*=0.45 (PHQ-9=10; moderate sD symptoms), *SMD*=0.51 (PHQ-9=15; moderately severe symptoms), and *SMD*=-0.65 (PHQ-9=20; severe symptoms). Response and deterioration rates conditional on baseline PHQ-9 values are presented in supplement S15.

Discussion

To our knowledge, this is the first IPD-MA to synthesize the effect of psychological intervention in sD across all major treatment formats and target groups. We find that interventions yield significant benefits up to 12 months, which includes a protective effect on symptom deterioration. Baseline depression and anxiety severity emerged as the most credible effect modifiers, indicating that effects are greatest for individuals who already experience more severe symptoms.

Our pooled post-test effect (*SMD*=-0.48) slightly exceed estimates of previous meta-analyses (SMD=-0.17 to −0.39)[12–16]. It should be noted that our synthesis included a considerably larger number of trials than these previous reviews (*k*=50 vs. *k*=5-32), and that our IPD-MA approach allowed to include trials with mixed populations as well. Furthermore, our results up to six (*SMD*=-0.28) and twelve months (*SMD*=-0.27) also indicate somewhat weaker benefits. Nevertheless, we can conclude that psychological intervention is an effective method to address sD at least up to one year.

Intervention effects up to 24 months are less certain. We could not ascertain significance for any outcome within this time frame, and we only found a 29% probability that effects on symptom severity were minimally important. We want to stress here that clinically irrelevant effects on a patient level may still be important on a population level. Looking at the control groups, for example, we find that 52 out of 100 individuals achieve close to symptom-free status up to 24 months, even without the treatment. Provision of the psychological interventions studied in this

meta-analysis would lead to an additional 5 individuals being symptom-free after two years.

Yet, given these very subtle effects (if existent at all), and the fact that an estimated 43% of individuals will not attain symptom-free status even when treated, long-term monitoring of the symptom course seems indicated, even when individuals with sD can be motivated to partake in a one-time psychological intervention. Future research may also put a greater emphasis on long-term intervention strategies, for example repeated booster sessions administered one year after the main treatment, to determine if this helps to maintain effects over a longer period.

Individuals with sD, by definition, do not (yet) suffer from a diagnosable MDD. Some individuals may also display only very mild symptoms, which do not necessarily transition into more severe symptoms, and can be transient[38,39]. This increases the importance to identify those for whom a psychological intervention is particularly helpful. Such benefits must also be viewed in the context of available health care resources, given that sD is even more prevalent than MDD[40] as well as potential risks of intervening, which includes the medicalization of individuals without a diagnosable mental disorder[41].

Therefore, a major strength of this IPD-MA is that we explored effect heterogeneity on a participant level. Targeted superlearning indicated treatment effects that are highly variable, including a substantial proportion of participants with no predicted benefits. Within two years, almost 40% of our sample were estimated to fare no better under treatment than under control. This underlines the relevance of our moderator analysis, in which initial symptom severity emerged as the most robust predictor. Thus, in clinical practice, symptom severity may be the most relevant yardstick by which the benefits of intervening in individuals with sD can be determined. We found the largest treatment effect estimates in individuals with at least moderate symptoms (*SMD*=-0.45 to −0.65; PHQ-9≥10). For such individuals, psychological intervention seems strongly indicated.

Minimally relevant benefits were predicted even for individuals with very mild symptoms (i.e., PHQ-9 scores of 5). However, effects at this symptom level correspond with an NNT of 11, meaning that almost a dozen individuals need to be treated to see one additional case of improvement. One could argue that reliable improvement is less relevant among individuals with mild symptoms, and that the prevention of symptom deterioration is more important. Yet, we found that only few individuals with low PHQ-9 scores reliably deteriorate (supplement S15), suggesting the NNT for this outcome would be even higher.

For individuals with very mild symptoms, interventions in this IPD-MA would therefore need to be widely disseminated to have a meaningful impact at the population level. This may be challenging, given that most of the investigated treatments were face-to-face therapies with limited scalability. Digital interventions may be a more suitable option, and can be most easily disseminated as pure self-help, although often at the cost of lower effectiveness[42,43]. A more time-honored approach for mild symptoms could be watchful waiting, whereby professionals monitor individuals' symptoms over a longer period[44], and to intervene only when symptoms persist or

worsen. Some of the stepped-care interventions included in this IPD-MA already implemented comparable methods.

Lastly, we also want to point at some other variables for which we found tentative evidence of effect modification (>90% probability), including relationship status, treatment history, and sex. Such characteristics could be used as further stratification variables, but this would probably warrant further investigation in the context under study. No signs of effect modification were found for other relevant indicators, such as age, ethnicity, medical comorbidities, antidepressant use, or past MDD episodes. If true, this would underline the broad applicability of psychological interventions across various sD populations.

Our study has several limitations. First, we could not obtain IPD from all eligible trials (29 out of 79 studies). However, our analysis including both IPD and aggregate-data trials largely corroborated our main analysis. Second, individualized effect estimates of our superlearning approach should be interpreted with caution, since they depend on counterfactual information that cannot be directly observed; and because results may strongly hinge on the covariate information available in each study. Not all putative moderators defined in our initial protocol could be considered due to their absence in the provided IPD. This includes variables such as traumatic events, childhood adversity, self-esteem, or diet. In our moderator analysis, we also only examined variables one-by-one, instead of developing a more complex multivariable prediction model[45]. However, such approaches also come with a greater risk of detecting spurious relationships[46], and can be difficult to interpret from a clinical perspective. Furthermore, 26% of the included studies focused on older adults, and the mean age of our sample was therefore rather high (M=52.8). This may restrict the generalizability of our findings to other populations. A more severe limitation is that only four trials (8%) were conducted in low- and middle-income countries (LMICs; China and Mexico). More studies are needed to examine if psychological interventions for sD are equally effective in LMICs, which is where 80% of all people with mental disorders live[47].

Conclusions

Our findings support the routine provision of psychological interventions in individuals with sD, especially those who already experience moderate depressive symptoms. Minimally important benefits may even emerge among individuals with very mild symptoms but should be weighed against available healthcare resources, and potential risks of intervening. More research is also needed to examine how treatment benefits can be sustained over several years.

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References

1. GBD 2019 Mental Disorders Collaborators. Global, regional, and national burden of 12 mental disorders in 204 countries and territories, 1990–2019: a systematic analysis for the Global Burden of Disease Study 2019. The Lancet Psychiatry. 2022;9(2):137-150.
2. Chesney E, Goodwin GM, Fazel S. Risks of all-cause and suicide mortality in mental disorders: a meta-review. World Psychiatry. 2014;13(2):153-160. doi:10.1002/wps.20128
3. Vos T, Abajobir AA, Abate KH, et al. Global, regional, and national incidence, prevalence, and years lived with disability for 328 diseases and injuries for 195 countries, 1990–2016: a systematic analysis for the Global Burden of Disease Study 2016. The Lancet. 2017;390(10100):1211-1259.
4. Association AP. Clinical practice guideline for the treatment of depression across three age cohorts. Published online 2019.
5. Gabriel FC, Melo DO de, Fráguas R, Leite-Santos NC, Silva RAM da, Ribeiro E. Pharmacological treatment of depression: A systematic review comparing clinical practice guideline recommendations. PLOS ONE. 2020;15(4):e0231700. doi:10.1371/journal.pone.0231700
6. Andrews G, Issakidis C, Sanderson K, Corry J, Lapsley H. Utilising survey data to inform public policy: Comparison of the cost-effectiveness of treatment of ten mental disorders. British Journal of Psychiatry. 2004;184(JUNE):526-533. doi:10.1192/bjp.184.6.526
7. Zhang R, Peng X, Song X, et al. The prevalence and risk of developing major depression among individuals with subthreshold depression in the general population. Psychological Medicine. 2023;53(8):3611-3620.
8. Cuijpers P, Vogelzangs N, Twisk J, Kleiboer A, Li J, Penninx BW. Differential mortality rates in major and subthreshold depression: meta-analysis of studies that measured both. The British Journal of Psychiatry. 2013;202(1):22-27. doi:10.1192/bjp.bp.112.112169
9. Goldney RD, Fisher LJ, Dal Grande E, Taylor AW. Subsyndromal depression: prevalence,use of health services and quality of life in an Australianpopulation. Soc Psychiatry Psychiatr Epidemiol. 2004;39(4):293-298. doi:10.1007/s00127-004-0745-5
10. Cuijpers P, Smit F, Oostenbrink J, De Graaf R, Ten Have M, Beekman A. Economic costs of minor depression: a population-based study. Acta Psychiatrica Scandinavica. 2007;115(3):229-236. doi:10.1111/j.1600-0447.2006.00851.x
11. Volz HP, Stirnweiß J, Kasper S, Möller HJ, Seifritz E. Subthreshold depression - concept, operationalisation and epidemiological data. A scoping review. Int J Psychiatry Clin Pract. 2023;27(1):92-106. doi:10.1080/13651501.2022.2087530
12. Cuijpers P, Koole SL, Dijke A van, Roca M, Li J, Reynolds CF. Psychotherapy for subclinical depression: meta-analysis. The British Journal of Psychiatry. 2014;205(4):268-274. doi:10.1192/bjp.bp.113.138784
13. Edge D, Watkins ER, Limmond J, Mugadza J. The efficacy of self-guided internet and mobile-based interventions for preventing anxiety and depression–A systematic review and meta-analysis. Behaviour Research and Therapy. Published online 2023:104292.
14. Huang K, You S, Yue X, et al. Effects of non-pharmacological interventions on depressive symptoms and risk of major depressive disorder in adults with subthreshold depression: A systematic review and meta-analysis. Psychiatry Res. 2023;326:115333. doi:10.1016/j.psychres.2023.115333
15. Reins JA, Buntrock C, Zimmermann J, et al. Efficacy and moderators of internet-based interventions in adults with subthreshold depression: an individual participant data meta-analysis of randomized controlled trials. Psychotherapy and Psychosomatics. 2021;90(2):94-106.
16. Rigabert A, Motrico E, Moreno-Peral P, et al. Effectiveness of online psychological and psychoeducational interventions to prevent depression: Systematic review and meta-analysis of randomized controlled trials. Clinical Psychology Review. 2020;82:101931.
17. Cuijpers P, Pineda BS, Quero S, et al. Psychological interventions to prevent the onset of depressive disorders: A meta-analysis of randomized controlled trials. Clinical Psychology Review. 2021;83:101955.
18. Buntrock C, Harrer M, Sprenger AA, et al. Psychological Interventions to Prevent the Onset of Major Depression: A Systematic Review Andn Individual Participant Data Meta-Analysis. Lancet Psychiatry. 2024;in press.

19. Riley RD, Fisher DJ. Using IPD Meta-Analysis to Examine Interactions between Treatment Effect and Participant-level Covariates. In: Individual Participant Data Meta-Analysis. John Wiley & Sons, Ltd; 2021:163-198. doi:10.1002/9781119333784.ch7
20. Conejo-Cerón S, Bellón JÁ, Motrico E, et al. Moderators of psychological and psychoeducational interventions for the prevention of depression: A systematic review. Clinical Psychology Review. 2020;79:101859. doi:10.1016/j.cpr.2020.101859
21. Ebert DD, Buntrock C, Reins JA, Zimmermann J, Cuijpers P. Efficacy and moderators of psychological interventions in treating subclinical symptoms of depression and preventing major depressive disorder onsets: protocol for an individual patient data meta-analysis of randomised controlled trials. BMJ open. 2018;8(3):e018582.
22. Stewart LA, Clarke M, Rovers M, et al. Preferred Reporting Items for a Systematic Review and Meta-analysis of Individual Participant Data: The PRISMA-IPD Statement. JAMA. 2015;313(16):1657-1665. doi:10.1001/jama.2015.3656
23. Kroenke K, Spitzer RL, Williams JB. The PHQ-9: validity of a brief depression severity measure. Journal of general internal medicine. 2001;16(9):606-613.
24. Wahl I, Löwe B, Bjorner JB, et al. Standardization of depression measurement: a common metric was developed for 11 self-report depression measures. J Clin Epidemiol. 2014;67(1):73-86. doi:10.1016/j.jclinepi.2013.04.019
25. Alonso J, Liu Z, Evans-Lacko S, et al. Treatment gap for anxiety disorders is global: Results of the World Mental Health Surveys in 21 countries. Depression and anxiety. 2018;35(3):195-208.
26. Hao X, Jia Y, Chen J, Zou C, Jiang C. Subthreshold Depression: A Systematic Review and Network Meta-Analysis of Non-Pharmacological Interventions. Neuropsychiatric Disease and Treatment. 2023;19:2149-2169. doi:10.2147/NDT.S425509
27. Cuijpers P, Miguel C, Harrer M, et al. Psychological treatment of depression: A systematic overview of a 'Meta-Analytic Research Domain.' Journal of Affective Disorders. Published online 2023.
28. Sterne JA, Savović J, Page MJ, et al. RoB 2: a revised tool for assessing risk of bias in randomised trials. bmj. 2019;366.
29. Jacobson NS, Truax P. Clinical significance : A statistical approach to defining meaningful change in psychotherapy research. In: Methodological Issues & Strategies in Clinical Research. American Psychological Association; 1992:631-648. doi:10.1037/10109-042
30. Clark TP, Kahan BC, Phillips A, White I, Carpenter JR. Estimands: bringing clarity and focus to research questions in clinical trials. BMJ open. 2022;12(1):e052953.
31. Cristea IA, Vecchi T, Cuijpers P. Top-down and bottom-up pathways to developing psychological interventions. JAMA psychiatry. 2021;78(6):593-594.
32. Rücker G, Schwarzer G, Carpenter JR, Binder H, Schumacher M. Treatment-effect estimates adjusted for small-study effects via a limit meta-analysis. Biostatistics. 2011;12(1):122-142.
33. McShane BB, Böckenholt U, Hansen KT. Adjusting for publication bias in meta-analysis: An evaluation of selection methods and some cautionary notes. Perspectives on Psychological Science. 2016;11(5):730-749.
34. Duval S, Tweedie R. A nonparametric "trim and fill" method of accounting for publication bias in meta-analysis. Journal of the american statistical association. 2000;95(449):89-98.
35. Cho S, Preacher KJ, Yaremych HE, Naveiras M, Fuchs D, Fuchs LS. Modelling multilevel nonlinear treatment-by-covariate interactions in cluster randomized controlled trials using a generalized additive mixed model. Brit J Math & Statis. 2022;75(3):493-521. doi:10.1111/bmsp.12265
36. Wood SN. Just Another Gibbs Additive Modeler: Interfacing JAGS and mgcv. Journal of Statistical Software. 2016;75:1-15. doi:10.18637/jss.v075.i07
37. Cuijpers P, Turner EH, Koole SL, van Dijke A, Smit F. What Is the Threshold for a Clinically Relevant Effect? The Case of Major Depressive Disorders. Depression and Anxiety. 2014;31(5):374-378. doi:10.1002/da.22249
38. Hermens MLM, van Hout HPJ, Terluin B, et al. The prognosis of minor depression in the general population: a systematic review. General Hospital Psychiatry. 2004;26(6):453-462. doi:10.1016/j.genhosppsych.2004.08.006
39. Musliner KL, Munk-Olsen T, Eaton WW, Zandi PP. Heterogeneity in long-term trajectories of depressive symptoms: Patterns, predictors and outcomes. Journal of Affective Disorders. 2016;192:199-211. doi:10.1016/j.jad.2015.12.030
40. Cuijpers P, de Graaf R, van Dorsselaer S. Minor depression: risk profiles, functional disability, health care use and risk of developing major depression. Journal of Affective Disorders. 2004;79(1):71-79. doi:10.1016/S0165-0327(02)00348-8

41. Foulkes L, Andrews JL. Are mental health awareness efforts contributing to the rise in reported mental health problems? A call to test the prevalence inflation hypothesis. New Ideas in Psychology. 2023;69:101010.
42. Moshe I, Terhorst Y, Philippi P, et al. Digital interventions for the treatment of depression: A meta-analytic review. Psychological Bulletin. 2021;147(8):749.
43. Terhorst Y, Kaiser T, Brakemeier EL, et al. Heterogeneity of Treatment Effects in Internet- and Mobile-Based Interventions for Depression: A Systematic Review and Meta-Analysis. JAMA Network Open. 2024;7(7):e2423241. doi: 10.1001/jamanetworkopen.2024.23241
44. Cuijpers P. The Challenges of Improving Treatments for Depression. JAMA. 2018;320(24):2529-2530. doi:10.1001/jama.2018.17824
45. Efthimiou O, Seo M, Chalkou K, Debray T, Egger M, Salanti G. Developing clinical prediction models: a step-by-step guide. BMJ. 2024;386:e078276. doi:10.1136/bmj-2023-078276
46. Steyerberg EW. Overfitting and Optimism in Prediction Models. In: Steyerberg EW, ed. Clinical Prediction Models: A Practical Approach to Development, Validation, and Updating. Statistics for Biology and Health. Springer International Publishing; 2019:95-112. doi:10.1007/978-3-030-16399-0_5
47. Rathod S, Pinninti N, Irfan M, et al. Mental health service provision in low-and middle-income countries. Health services insights. 2017;10:1178632917694350.
48. Furukawa TA, Leucht S. How to obtain NNT from Cohen's d: comparison of two methods. PloS one. 2011;6(4):e19070.
49. Polley, E. C., Rose, S., & van der Laan, M. J. (2011). Super Learning. In M. J. van der Laan & S. Rose (Eds.), Targeted Learning: Causal Inference for Observational and Experimental Data (pp. 43–66). Springer. https://doi.org/10.1007/978-1-4419-9782- 1_3
50. Montoya, L. M., van der Laan, M. J., Luedtke, A. R., Skeem, J. L., Coyle, J. R., & Pe- tersen, M. L. (2022). The optimal dynamic treatment rule superlearner: Considera- tions, performance, and application to criminal justice interventions. *The International Journal of Biostatistics*.