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Review

Psychological intervention in individuals with subthreshold depression: individual participant data meta-analysis of treatment effects and moderators

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Background

It remains unclear which individuals with subthreshold depression benefit most from psychological intervention, and what long-term effects this has on symptom deterioration, response and remission.

Aims

To synthesise psychological intervention benefits in adults with subthreshold depression up to 2 years, and explore participant-level effect-modifiers.

Method

Randomised trials comparing psychological intervention with inactive control were identified via systematic search. Authors were contacted to obtain individual participant data (IPD), analysed using Bayesian one-stage meta-analysis. Treatment–covariate interactions were added to examine moderators. Hierarchical-additive models were used to explore treatment benefits conditional on baseline Patient Health Questionnaire 9 (PHQ-9) values.

Results

IPD of 10 671 individuals (50 studies) could be included. We found significant effects on depressive symptom severity up to 12 months (standardised mean-difference [s.m.d.] = −0.48 to −0.27). Effects could not be ascertained up to 24 months (s.m.d. = −0.18). Similar findings emerged for 50% symptom reduction (relative risk = 1.27–2.79), reliable improvement (relative risk = 1.38–3.17), deterioration (relative risk = 0.67–0.54) and close-to-symptom-free status (relative risk = 1.41–2.80). Among participant-level moderators, only initial depression and anxiety severity were highly credible ($P > 0.99$). Predicted treatment benefits decreased with lower symptom severity but remained minimally important even for very mild symptoms (s.m.d. = −0.33 for PHQ-9 = 5).

Conclusions

Psychological intervention reduces the symptom burden in individuals with subthreshold depression up to 1 year, and protects against symptom deterioration. Benefits up to 2 years are less certain. We find strong support for intervention in subthreshold depression, particularly with PHQ-9 scores ≥ 10. For very mild symptoms, scalable treatments could be an attractive option.

Keywords

Meta-analysis; depressive disorders; prevention; psychological treatments; precision medicine.

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 and 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 a 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]

Early intervention in depression

One way to meet this challenge is to intervene before patients develop MDD. Individuals with subthreshold depression may be the most promising target group for such an approach. Subthreshold depression can be defined as depressive symptoms that do not (yet) meet the diagnostic criteria of MDD. Such symptoms affect roughly 11% of the general population.[7] They are associated with elevated mortality,[8] increased healthcare

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utilisation,[9] substantial economic costs[10] and adverse effects on quality of life comparable to MDD.[11] Individuals with subthreshold depression are also three times more likely to develop MDD than healthy controls.[7] This underlines the importance of early intervention research. Intervening in this target group could be helpful to reduce the incidence of new MDD cases, and to treat already existing symptoms.

Prior evidence

Meta-analytic evidence suggests that psychological interventions are effective in subthreshold depression, yielding small to moderate benefits,[12–16] and that they can reduce the incidence of MDD by 19–43%.[17,18] Almost all of this evidence is based on aggregate data meta-analyses. We are aware of only 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.

Present study

A major strength of IPD meta-analyses (IPD-MAs) is that they can identify patient-specific effect modifiers.[19] This may be particularly attractive for psychological interventions in subthreshold depression, where findings on moderators remain inconclusive.[17,20] Robust moderators identified using IPD-MA could allow the stratification of existing care, by prioritising psychological intervention among individuals with subthreshold depression 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 the analysis of rates of treatment response, remission and symptom deterioration in a consistent way across all studies. Effects on such secondary outcomes remain understudied in subthreshold depression populations, as are the potential benefits of treatment over several years.

We therefore conducted an IPD-MA of psychological intervention effects in subthreshold depression, focusing on depressive symptom severity, 50% symptom reduction, reliable improvement, reliable symptom deterioration and achieving close to symptom-free status. We analysed both the short- and long-term benefits up to 2 years. Furthermore, we examined participant- and study-level moderators of differential treatment effects.

Method

Registration and protocol

This study has been registered with PROSPERO (no. 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 plan (SAP; doi.org/10.17605/osf.io/vba7f). 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 randomised trials in which (a) a psychological intervention (see definition in Supplementary Material S1) was compared with a control group (waitlist, care as usual, psychoeducational material, placebo) with regard to (b) effects on depressive symptom severity, (c) as measured by a validated patient or clinician-rated instrument in (d) adults without MDD at baseline and (e) as confirmed by a standardised 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 subthreshold depression 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 9 (PHQ-9).[23,24]

Study identification

Eligible studies were identified by two independent researchers screening full texts of the Metapsy (www.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 libraries PubMed, Embase, PsycINFO and Cochrane Central Register of Controlled Trials (see Supplementary Material 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.

The first database search we used to identify trials was conducted on 10 January 2017. The date of the first data extraction from retrieved full texts was not recorded. Requests for IPD from eligible trial authors began on 22 February 2017. From 2017 onward, search updates were screened annually to include IPD of trials that had been published in the interim. The most recent search we screened was conducted in January 2024, so that all studies published up to 1 January 2024 could be considered in this IPD-MA.

Data collection and harmonisation

Corresponding authors of eligible articles were contacted to request permission to use their IPD. Authors who responded were asked to provide data on demographic, clinical, outcome-related 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 Supplementary Material S3).

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

Risk of bias

In each study, two independent reviewers assessed the risk of bias using Cochrane's revised tool to assess risk of bias in randomised trials.[28] We rated all studies as being at low risk of bias for the 'missing outcome data' criterion, because 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 symptom severity scores we derived the following additional outcomes: (a) 50% symptom reduction compared with baseline (response); (b) close to symptom-free status (remission, defined as scores equivalent to PHQ-9 < 5[23]); and (c) reliable improvement and (d) 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 maximise the number of eligible trials, thus optimising the statistical power for our examination of treatment–covariate interactions. Among eligible trials, a smaller subset ($k = 30$) also reported MDD onset as confirmed by diagnostic interviews. These preventive outcomes were examined in a previous study.[18]

Statistical analyses

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 (a) recalculated all effects using two-stage IPD-MA, (b) conducted a conventional meta-analysis that also included studies not providing IPD, (c) calculated effects excluding 'bottom-up' therapies[31] and stepped-care interventions and (d) ran analyses adjusting for potential small-study effects and/or selective publication.[32–34]

Moderator analyses focused on participant-level variables, which are typically not available in conventional meta-analyses, and come with a lower risk of ecological bias than aggregated study-level characteristics. Moderators were examined by extending the one-stage IPD-MA models, with symptom severity at the first post-treatment assessment point available in each study serving as the outcome. Additionally, we also examined study-level moderators of the effect. Last, we used an additive mixed model[35,36] to examine potentially non-linear interactions between treatment effects and baseline PHQ-9 scores. A detailed description of all statistical analyses is provided in Supplementary Material S4.

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, $n = 5470$; control, $n = 5201$) were included in the IPD-MA. Additional effect size data was available for $k = 11$ studies that did not provide IPD (1376 participants; intervention, 680; control, 696). Study references can be found in Supplementary Material S6. Supplementary Material S5 summarises the study search and inclusions.

Study characteristics

Table 1 provides characteristics of the included studies. 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 and missing outcome data are given in Supplementary Material S7 and S8, respectively. Most participants ($N = 7199$, 68%) were female and the mean age was $M = 52.79$ (s.d. = 18.72). The mean PHQ-9 score at baseline (directly recorded or converted using the common metric) was 8.78 (s.d. = 4.32). Most studies received a low risk of bias assessment (62%, $k = 31$). Eleven (22%) showed high overall risk.

Treatment effects

A forest plot displaying results on depressive symptom severity is given in Fig. 1. Psychological intervention reduced depressive symptom severity significantly at post-test (standardised mean difference [s.m.d.] = −0.48, 95% CrI = −0.63 to −0.33, $k = 47$), within 6 months (s.m.d. = −0.28, 95% CrI = −0.40 to −0.16, $k = 39$) and within 1 year (s.m.d. = −0.27, 95% CrI = −0.37 to −0.16, $k = 33$). No significant effect emerged among studies recording outcomes up to 2 years (s.m.d. = −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 s.m.d. = −0.24. This effect was determined as a minimally important 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 1 year and 28.9% up to 2 years.

Similar findings emerged for all other outcomes. From post-test up to 12 months, we found positive effects on 50% symptom reduction, reliable improvement and achieving close to symptom-free status (relative risk = 1.23–1.91). Interventions also had a protective effect on reliable symptom deterioration, reducing the risk by 23–32%. No significant effects could be ascertained for any of these outcomes up to 24 months. For all favourable outcomes, control group event rates 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 2 years. Table 2 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 Supplementary Material S9–S13).

Effect modifiers

Table 3 shows the results for participant-level moderators. Only baseline depression and anxiety symptom severity emerged as highly credible effect modifiers (posterior tail probabilities >99%). For both, higher initial symptom severity predicted 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 Supplementary Material S14. Among study-level variables, only target group and intervention type were significant moderators. Smaller effects were found in general adult, older adult, chronic pain, diabetes and pregnant women populations (s.m.d. = −0.15 to −0.39), while higher benefits emerged in university students (s.m.d. = −0.59) and informal caregivers (s.m.d. = −1.35). Across intervention types, the largest effects were found for behavioural activation (s.m.d. = −0.72) and CBT-based treatments (s.m.d. = −0.56). The subgroup-specific effect among studies with a low revised Cochrane risk-of-bias tool for randomised trials (RoB) rating was s.m.d. = −0.51 (95% CrI = −0.70 to −0.33).

Figure 2 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

Table 1 Study characteristics

Study	Target group	Age range (years)	Inclusion criteria	Conditions	*n*	Delivery	Sessions	Country	Quality criteria[a] D1	D2	D3	D4	D5	Overall
Albert, 2019	Older adults	61–103	PHQ ≥ 1, 3MS > 80, need for assistance in daily tasks; no (MDD or anxiety disorder in past 12 months current antidepressant or anxiolytics use, neuropsychiatric disorders, drug or alcohol treatment in past 12 months)	PST Enhanced TAU	51 51	Face to face	6–8	USA	+	+	+	+	+	+
Allart, 2007	Adults	20–65	BDI ≥ 10; no MDD, psychiatric diagnosis or lifetime history of bipolar disorder	CBT CAU	69 42	Face to face	12	Netherlands	?	+	+	+	+	?
Almeida, 2020	Older adults	65–91	Positive Whooley screening, residence in regional or remote regions of Western Australia; no MDD, suicidal planning, significant sensory or cognitive impairment or severe physical illness	BA Waitlist	154 153	Other	–	Australia	?	+	+	?	+	?
Apil, 2014	Older adults	55–91	Received psychological and/or pharmacological treatment for depression in the past; no MDD, psychotic disorders, dysthymic disorder, bipolar disorder, primary anxiety disorder, substance abuse or dependence or frailty	Stepped care CAU	39 52	Other	12	Netherlands	?	+	+	+	?	?
Barrett, 2001	Adults	18–60	Age 18–60 years, minor depression (3/4 symptoms >4 weeks), HDRS ≥ 10; no MDD, psychosis, schizophrenia, schizoaffective disorder, bipolar affective disorder, alcohol or other substance abuse with past 6 months, antisocial or borderline personality disorder, suicidal risk, cognitive impairment, medical illness with less than 6 months to live, current treatment with>50 mg amitriptyline or equivalent	PST Placebo	72 76	Face to face	6	USA	+	+	+	?	?	?
Basanovic, 2019	Adults	45–99	PHQ-9 ≥ 5 and ≤ 14; no MDD, psychotic disorders, bipolar disorder, severe physical illness, substance abuse or dependence, cognitive or visual impairment or suicidal planning	CBM Tasks without CBM	102 100	Internet	44	Australia	+	+	+	+	+	+
Batterham, 2017	Adults	18–64	PHQ-9 > 4 and < 20, significant insomnia symptoms; no MDD, lifetime bipolar disorder, psychotic disorders, suicidal planning or regular night-time sleep patterns	CBT Health information	574 575	Internet	6	Australia	+	+	+	+	+	+
Bø, 2023	Adults	18–71	At least two previous episodes of MDD, currently in remission; no current or former neurological disorders, psychosis, bipolar spectrum disorders, substance use disorders, attention deficit disorder or head trauma	ABM Sham ABM	120 126	Other		Norway	+	–	+	+	?	–
Buntrock, 2015	Adults	1978	CES-D ≥ 16; no MDD in past 6 months, current psychotherapy or in the past 6 months, suicidal planning, bipolar disorder or psychotic disorders	CBT Information on depression	202 204	Internet	6	Germany	+	+	+	+	+	+
Cook, 2019	University students	18–24	PSWQ ≥ 50, RRS ≥ 40; no MDD, current and significant substance abuse or dependence, current symptoms/diagnosis of psychosis or bipolar disorder, current psychological therapy or active suicide risk	CBT Waitlist	82 77	Internet	6	UK	+	+	+	+	+	+
Dozeman, 2012	Nursing home residents	61–100	CES-D ≥ 8; no MDD, anxiety disorder or substantial cognitive impairment	Stepped care CAU	90 89	Other		Netherlands	+	+	+	+	+	+
Ebert, 2018	Adults	20–75	CES-D ≥ 16; no MDD	CBT Waitlist	102 102	Internet	6	Germany	+	+	+	+	+	+
Furukawa, 2012	Employees	23–57	BDI-II ≥ 10, K6 ≥ 9; no MDD in the past month	CBT Waitlist	58 60	Telephone	8	Japan	+	+	+	–	+	–
Gilbody, 2017	Older adults	64–96	≥ 2 depressive symptoms (MINI)	BA CAU	344 361	Telephone	8	UK	+	+	+	–	+	–
Hankin, 2023	Pregnant women	18–42	25 weeks' gestational age or less, singleton pregnancy, EPDS score ≥10; no current illicit drug or methadone use, major health conditions requiring invasive treatments (e.g. dialysis, blood transfusions, chemotherapy), current or past psychosis or mania, current cognitive behavioural therapy or IPT	IPT Enhanced CAU	115 119	Face to face	8	USA	+	+	+	+	+	+

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Haringsma, 2006	Older adults	53–85	No concurrent therapy	CBT CAU	31 26	Face to face	10	Netherlands	?	+	+	–	+	–
Hoorelbeke, 2017	Adults	23–65	No MDD in past 6 months, history of bipolar disorder, psychosis, substance abuse, brain injury or acute treatment ≥1–3 weeks	CCT Control training	9 10	Internet	10	Belgium	+	+	+	+	+	+
Imamura, 2014	Employees	21–62	No MDD in past month, lifetime bipolar disorder, ≥15 sick days for mental health in past 3 months or medical treatment for mental health in past month	CBT Stress management information + waitlist	213 208	Internet	6	Japan	+	+	+	–	+	–
Irwin, 2022	Older adults	60–93	Age ≥60 years, insomnia disorder by DSM-IV, PSQI > 5, CESD < 4; no MDD (DSM-IV or DSM-5) within past 12 months	CBT Sleep education	94 87	Face to face	8	USA	+	+	+	+	+	+
Karyotaki, 2022	University students	18–27	PHQ-9 > 4 and < 14 or GAD-7 > 4 and < 14; no bipolar disorder or psychological treatment in past 12 months	CBT TAU	19 29	Internet	7	Netherlands	+	+	+	+	+	+
Klein, 2016	Adults	18–65	PHQ-9 ≥ 5 and ≤ 14; no suicidal planning, lifetime diagnosis of bipolar disorder or schizophrenia	CBT Waitlist	355 368	Internet	10	Germany	+	+	+	+	+	+
Konnert, 2009	Nursing home residents	65–97	GDS > 9; no MDD, substantial physical or cognitive impairment	CBT TAU	32 26	Face to face	13	Canada	–	–	+	–	+	–
Krebber, 2016	Adults	40–83	Treatment for UICC stage I–IV lung or head and neck carcinoma, HADS-D > 7, HADS-A > 7 or HADS-total > 14; no neurological diseases causing cognitive dysfunction, motivation for psychological therapy, current treatment for psychiatric disorder (<2 months ago), suicide risk, psychotic and/or manic signs	Stepped care CAU	61 60	Other	6	Netherlands	?	+	+	?	?	?
Lara, 2010	Pregnant women	18–43	CES-D ≥ 16 and/or self-reported history of depression, ≤26 weeks pregnant; no MDD, substance abuse or suicidal planning in past 6 months, bipolar disorder	Psychoeducation course CAU	200 95	Face to face	8	Mexico	+	+	+	+	+	+
Le, 2011	Pregnant women	17–37	CES-D ≥ 16 and/or self-reported history of depression, ≤24 weeks gestation; no MDD, substance abuse, psychosis, significant medical condition or psychosocial problems	CBT CAU	112 105	Face to face	8	USA	+	+	+	+	+	+
Mossey, 1996	Older adults	60–91	GDS > 10, no MDD	IPC CAU	52 49	Face to face	10	USA	?	+	+	–	+	–
Muñoz, 2007	Pregnant women	18–35	CES-D ≥ 16 and/or past history of MDE, 12–32 weeks pregnant; no MDD, substantial medical illness or substance abuse	CBT CAU	21 20	Face to face	12	USA	+	+	+	–	+	–
Nobis, 2015	Diabetes patients	19–80	CES-D ≥ 23	CBT Information on depression	14 16	Internet	6	Germany	+	+	+	+	+	+
Oosterbaan, 2013	Adults	19–82	Common DSM-IV mental disorder (panic disorder, agoraphobia, social phobia, specific phobia, GAD, unipolar major and minor depressive disorder, dysthymia or stress-related adjustment disorder); no dependence on alcohol or drugs, dementia, psychotic disorder, bipolar disorder, undergoing treatment with psychotropic drugs (except for benzodiazepines), CBT or interpersonal therapy for present episode	Stepped care CAU	26 28	Face to face		Netherlands	+	+	+	+	?	?
Otero, 2014	Informal caregivers	31–76	CES-D ≥ 16, female; no current or former MDD	PST CAU	89 84	Face to face	5	Spain	+	+	+	+	+	+
Pibernik-Okanović, 2015	Diabetes patients	38–65	PHQ-2 ≥1; no clinical depression, current psychiatric treatment, advanced diabetes complications	Pychoeducation course Physical exercise Enhanced TAU	74 66 69	Face to face	6	Croatia	+	+	+	+	+	+
Pols, 2017	Diabetes patients	36–94	PHQ-9 ≥ 6, diagnosis of type 2 diabetes and/or coronary heart disease; no MDD, cognitive or visual impairment, psychotic disorders, terminal illness, antidepressant treatment, loss in past 6 months, history of suicide attempts, bipolar disorder, borderline personality disorder, or pregnancy	Stepped care CAU	90 133	Other	7	Netherlands	+	+	+	+	+	+

(Continued)

Table 1 *(Continued)*

Study	Target group	Age range (years)	Inclusion criteria	Conditions	*n*	Delivery	Sessions	Country	Quality criteria[a]					
									D1	D2	D3	D4	D5	Overall
Pot, 2010	Older adults	51–90	>50 years, CES-D ≥ 5; no depressive disorder, psychotropic or psychological treatment	Life review Educational video	83 88	Face to face	12	Netherlands	+	+	+	–	+	–
Reynolds, 2014	Older adults	50–96	CES-D ≥ 11; no MDD in past 12 months, dementia, substance abuse in past 12 months, history of bipolar disorder, psychotic disorders or neurodegenerative disorders	PST Dietary coaching	125 122	Face to face	6–8	USA	+	+	+	+	+	+
Rovner, 2007	Older adults	65–96	Recent bilateral visual impairment by age-related macular degeneration; no MDD or treatment, cognitive impairment or confounding eye conditions	PST CAU	105 101	Face to face	6	USA	+	+	+	+	+	+
Sanabria-Mazo, 2023	Chronic pain patients	19–70	Diagnosis of chronic low back pain ≥3 months, pain intensity >4 points out of 10 on a numeric rating scale in last week, PHQ-9 ≥ 10 in last 2 weeks; no presence of cognitive impairment according to medical history, previous (last year) or current psychological therapy, diagnosis of severe psychiatric disorder or substance dependence/abuse, radiculopathy, involvement in litigation with the healthcare system or scheduled surgical intervention and inability to attend group sessions	ACT BA TAU	15 18 23	Telephone/ video conference	8	Spain	+	+	+	+	+	+
Sander, 2020	Chronic pain patients	24–78	PHQ-9 ≥ 5, diagnosis of chronic back pain (≥6 months); no MDD or psychotherapy in past 6 months, persistent depressive disorder, bipolar disorder, suicidal ideation or attempts in past 5 years	CBT TAU	149 146	Internet	6–9	Germany	+	+	+	+	+	+
Spek, 2007	Older adults	50–75	EDS > 12; no MDD according to DSM-IV, psychiatric disorder, suicidal ideation or age 50–75 years	CBT CBT Waitlist	102 99 100	Internet Face to face	8–10	Netherlands	+	+	+	–	+	–
van Bastelaar, 2011	Diabetes patients	19–82	CES-D ≥ 16, diabetes; no suicide attempts, current suicidal ideation, bipolar depression, psychotic disorder, pregnancy or loss of a significant other within past 6 months	CBT Waitlist	54 55	Internet	8	Netherlands	+	+	+	+	+	+
van't Veer, 2009	Older adults	76–95	CES-D ≥ 16; no depressive or anxiety disorder in past 12 months or substantial cognitive impairment	Stepped care CAU	86 84	Other	7	Netherlands	+	+	+	+	+	+
Vázquez, 2012	University students	18–42	CES-D ≥ 16; no lifetime MDD, intention to move residence within past 9 months, dysthymia, bipolar disorder, cyclothymia, anorexia, psychotic disorders, substance abuse, panic disorder, obsessive–compulsive disorder, somatisation disorder, hypochondria, undifferentiated somatoform disorder or risk for suicide	CBT Relaxation	70 63	Face to face	8	Spain	+	+	+	+	+	+
Vázquez, 2016	Informal caregivers	32–79	CES-D ≥ 16, women, primary caregiver of a dependent family member; no current or past MDE as determined by DSM-IV criteria, psychiatric or psychological treatment in the past 2 months, other axis-I disorders that might interfere with fulfillment of the objectives of the study (e.g. bipolar disorder I and II or psychotic disorders), presence of psychological or medical conditions that require immediate intervention (e.g. to be at risk for suicide) or interfere with study participation (e.g. mental deficiency, significant cognitive deterioration), anticipation of a change of residence or institutionalisation, or severe or terminal prognosis of a relative	CBT CAU	88 82	Face to face	5	Spain	+	+	+	+	?	?
Vázquez, 2017	Informal caregivers	42–75	CES-D ≥ 16; no current or lifetime MDD, psychological or psychopharmacological treatment in past 2 months, severe mental or medical conditions, severe or terminal prognosis of dependee or intention to move residence	BA CBT CAU	22 20 19	Telephone/ video conference	5	Spain	+	+	+	+	+	+
Vázquez, 2022	Informal caregivers	25–76	CES-D ≥ 16; no current or lifetime MDD, psychological or psychopharmacological treatment in past 2 months, severe mental or medical conditions, severe or terminal prognosis of dependee or intention to move residence	BA CBT CAU	70 69 80	Telephone/ video conference	5	Spain	?	+	+	–	+	–

(Continued)

Vázquez, 2023	Informal caregivers	27–72	CES-D ≥ 16, non-professional caregiver of a dependent person, having a smartphone; no current or past MDE as determined by DSM-V criteria, psychological or psychopharmacological treatment in past 2 months, other disorders that could act as confounding factors (i.e. symptoms due to substance use or medical conditions), serious mental or medical disorders that required immediate intervention or made it impossible to participate, imminent terminal prognosis of the care recipient or anticipation of a change of residence/institutionalisation of the care recipient during the study	CBT CBT Information on depression	58 54 63	Internet Internet/video conference	5	Spain	+	+	+	+	+	+
Willemse, 2004	Adults	18–66	Subthreshold depression (≥1 core symptom, 1–3 current symptoms (Instel screening instrument); no MDD, treatment in past 12 months, hearing or language difficulties, life-threatening illness, learning disability, suicidal risk, psychotic symptoms, schizophrenia or dementia (dysthymia, bipolar disorder, social phobia, agoraphobia or panic disorder in past 12 months)	CBT CAU	107 109	Other	–	Netherlands	+	+	+	+	+	+
Williams, 2000	Older adults	60–90	Age ≥60 years, minor depression (3/4 symptoms >4 weeks), HDRS ≥ 10; no MDD, psychosis, schizophrenia, schizoaffective disorder, bipolar affective disorder, alcohol or other substance abuse with past 6 months, antisocial or borderline personality disorder, suicidal risk, cognitive impairment, medical illness with <6 months to live or current treatment with >50 mg amitriptyline or equivalent	PST Placebo	130 132	Face to face	6	SA	+	+	+	?	?	?
Wong, 2018	Adults	53–85	5 ≤ PHQ-9 ≤ 9 ; no dysthymia with subthreshold depressive symptoms that had lasted for 2 years or more within the past 6 months, lifetime history of other psychiatric disorders (GAD, psychosis, schizophrenia or bipolar affective disorder), alcohol or substance abuse, serious suicidal risk, medical illness with a prognosis of <6 months to live, current treatments (antidepressants or other psychotropic medications, or enrollment in any form of psychological interventions) for any depressive disorders or symptoms or inability to read or write	BA CAU	115 116	Face to face	8	China	+	+	+	+	+	+
Yang, 2015	University students	18–22	BDI-II ≥ 14; no MDD, bipolar disorder, schizophrenia, other mental disorders, current psychotherapy or psychotropic medication	CBM Attention control Assessment only	27 27 23	Other	8	China	+	+	+	+	+	+
Zhang, 2014	Adults	21–70	CES-D ≥ 16 or HADS-A ≥ 6; no MDD or anxiety disorders	Stepped care CAU	121 119	Other	6	China	+	+	+	+	+	+

3MS, modified mini-mental state examination; ABM, attentional bias modification; ACT, acceptance and commitment therapy; BA, behavioural activation; BDI, Beck Depression Inventory; CAU, care as usual; CBM, cognitive bias modification; CBT, cognitive behaviour therapy; CES-D, Center for Epidemiological Studies' Depression Scale; EPDS, Edinburgh Postnatal Depression Scale; GAD, generalised anxiety disorder; GDS, Geriatric Depression Scale; HADS-A/D, Hospital Anxiety and Depression Scale (anxiety/depression subscale); HDRS, Hamilton Rating Scale for Depression; IPC, interpersonal counselling; IPT, interpersonal psychotherapy; K6, Kessler Non-specific Distress Scale; MDE, major depressive episode; MINI, mini-international neuropsychiatric interview; PHQ, Patient Health Questionnaire; PST, problem-solving therapy; PSQI, Pittsburgh Sleep Quality Index; RRS, Ruminative Response Scale; TAU, treatment as usual; UICC, Union for International Cancer Control.

a. Signs in this column represent judgements based on the revised Cochrane risk-of-bias tool for randomised trials (RoB 2) on five domains: randomisation process (D1), deviation from the intervention (D2), missing outcome data (D3), measurement of the outcome (D4) and selection of the reported results (D5; in this order); the column 'All' represents the overall judgement regarding risk of bias. All studies were rated as fulfilling the 'missing data' criterion, because multiple imputation could be used in all studies to handle missing data. Rating options are 'low risk of bias' (+), 'high risk of bias' (–) or 'some concerns' (?).

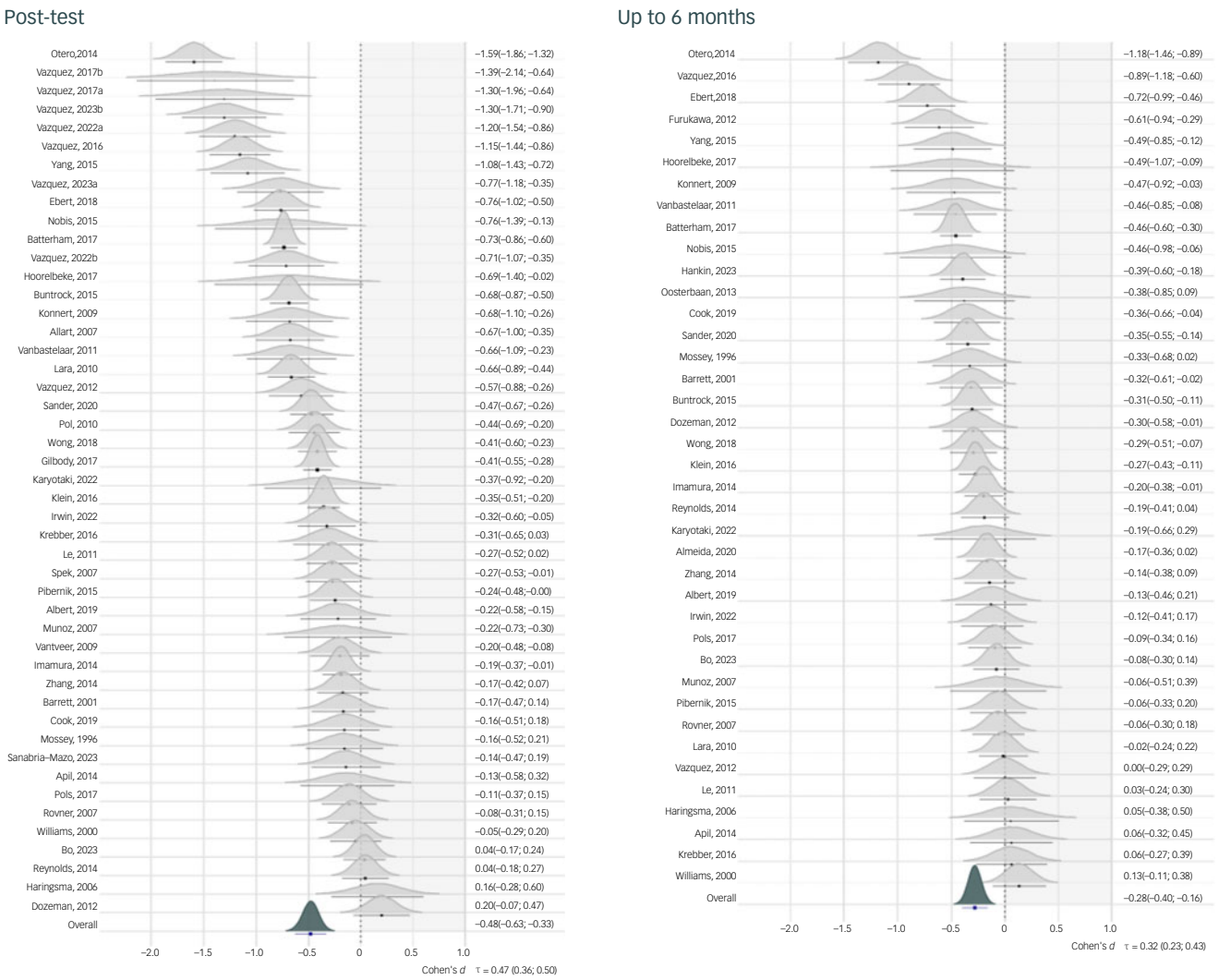

Fig. 1 Forest plot for effects on depressive symptom severity at different assessment points. All effects are expressed as the standardised mean difference (s.m.d.; Cohen's *d*). Study densities represent the estimated model-based effect, not empirical values of the s.m.d. found in the original studies.

with higher initial PHQ-9 values. Predicted treatment effects at established PHQ-9 cut-offs[23] were s.m.d. = −0.33 (PHQ-9 = 5; lower cut-off for subthreshold depression), s.m.d. = −0.45 (PHQ-9 = 10; moderate subthreshold depression symptoms), s.m.d. = −0.51 (PHQ-9 = 15; moderately severe symptoms) and s.m.d. = −0.65 (PHQ-9 = 20; severe symptoms). Response and deterioration rates conditional on baseline PHQ-9 values are presented in supplementary material S15.

Discussion

To our knowledge, this is the first IPD-MA to synthesise the effect of psychological intervention in subthreshold depression 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 (s.m.d. = −0.48) slightly exceeds estimates of previous meta-analyses (s.m.d. = −0.17 to −0.39).[12–16] It should be noted that our synthesis included a considerably larger number of trials than did these previous reviews ($k = 50$ *v.* 5–32), and that our IPD-MA approach also allowed the inclusion of trials with mixed populations. Furthermore, our results up to 6 months (s.m.d. = −0.28) and 12 months (s.m.d. = −0.27) also indicate somewhat weaker benefits. Nevertheless, we can conclude that psychological intervention is an effective method to address subthreshold depression for at least up to 1 year.

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

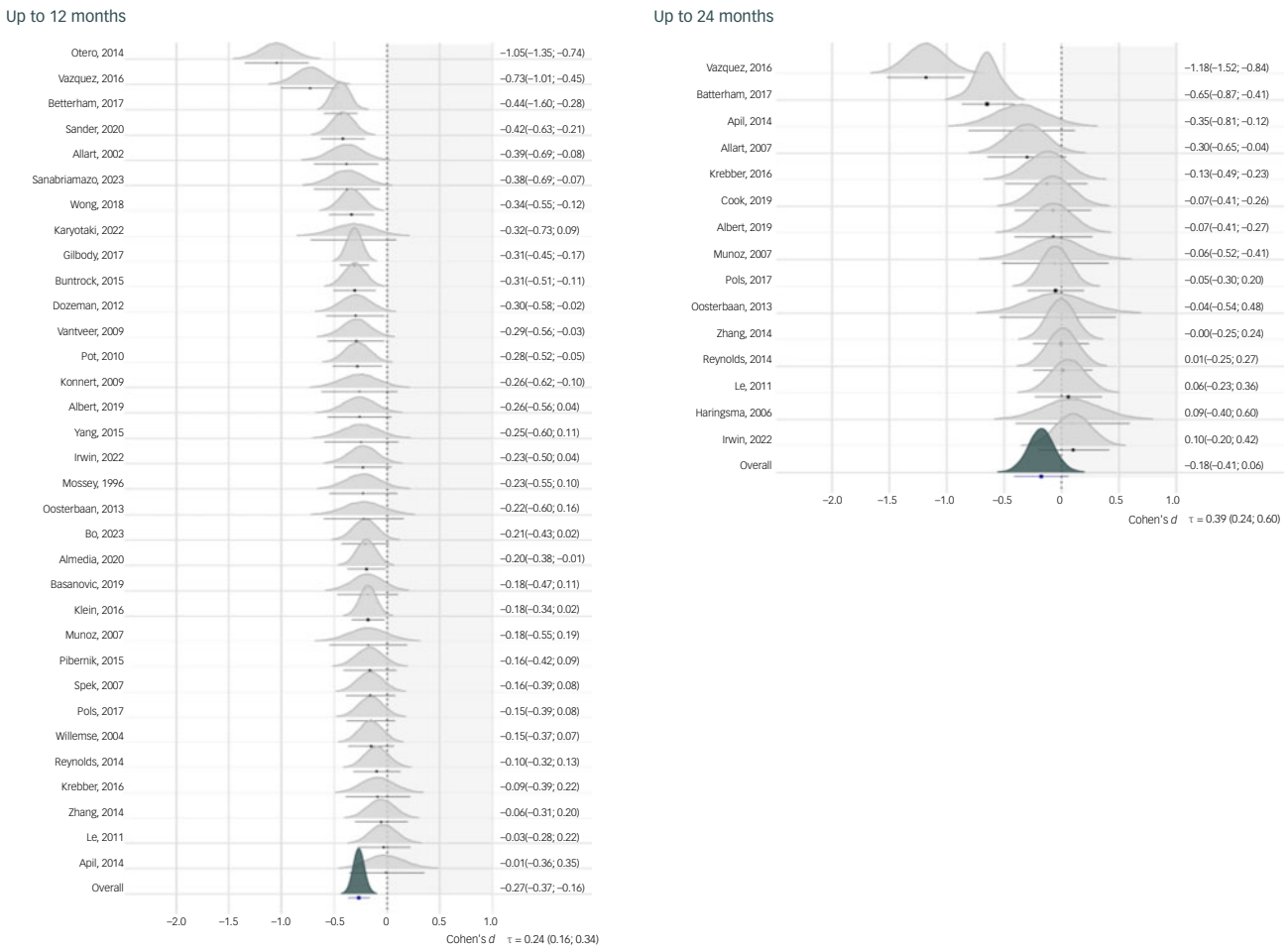

Fig. 1 (Continued).

2 years. On a global scale, this would still mean that thousands of additional individuals could achieve remission, presuming that treatments are widely disseminated.

Nevertheless, 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 subthreshold depression 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 1 year following the main treatment, to determine whether this helps to maintain effects over a longer period.

Individuals with subthreshold depression, 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 of identifying those for whom a psychological intervention is particularly helpful. Such benefits must also be viewed in the context of available healthcare resources, given that subthreshold depression is even more prevalent than MDD[40], as well as potential risks of intervening, which includes the medicalisation of individuals without a diagnosable mental disorder.[41]

To this end, one major benefit of this IPD-MA is its ability to explore moderators on a participant level. We found that initial symptom severity was the most robust predictor of treatment effects. Thus, in clinical practice, symptom severity may be the most relevant yardstick by which the benefits of intervention in individuals with subthreshold depression can be determined. We found the largest effect estimates in individuals with at least moderate symptoms (s.m.d. = −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 = 5). However, effects at this symptom level correspond with a number needed to treat (NNT) of 11, meaning that almost a dozen individuals need to be treated to achieve 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. Nevertheless, we found that only a few individuals with low PHQ-9 scores reliably deteriorate (Supplementary Material S15), suggesting that 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 could 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-honoured 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

Table 2 Pooled effects on depressive symptom severity, response and deterioration

Symptom status	*k*	Participants			Effect size (95% CrI)	NNT[a]	95% PI	$\hat{\tau}$ (95% CrI)	Relative risk[b]	Event rate[b]	
		Total	IGs	CGs						Intervention	Control
Depressive symptom severity (s.m.d.)											
Post-test	47	9418	4875	4543	–0.48 (–0.63; –0.33)	6.61	(–1.44; 0.48)	0.47 (0.36; 0.60)	–	–	–
Up to 6 months	39	8218	4152	4066	–0.28 (–0.40; –0.16)	11.12	(–0.94; 0.38)	0.32 (0.23; 0.43)	–	–	–
Up to 12 months	33	7740	3903	3837	–0.27 (–0.37; –0.16)	11.52	(–0.77; 0.23)	0.24 (0.16; 0.34)	–	–	–
Up to 24 months	15	3163	1597	1566	–0.18 (–0.41; 0.06)	15.36	(–1.05; 0.70)	0.39 (0.24; 0.60)	–	–	–
50% symptom reduction (odds ratio)											
Post-test	47	9418	4875	4543	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	8218	4152	4066	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	7740	3903	3837	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	3163	1597	1566	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 (odds ratio)[c]											
Post-test	42	8701	4512	4189	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	7267	3674	3593	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	7598	3833	3765	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	3163	1597	1566	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 (odds ratio)											
Post-test	47	9418	4875	4543	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	8218	4152	4066	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	7740	3903	3837	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	3163	1597	1566	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 (odds ratio)											
Post-test	47	9418	4875	4543	0.54 (0.35; 0.73)	50	(0.16; 1.75)	0.56 (0; 1.06)	0.68 (0.59; 0.79)	4% (3.6%; 4.7%)	6% (5.6%; 6.3%)
Up to 6 months	39	8218	4152	4066	0.67 (0.47; 0.91)	71.43	(0.26; 1.75)	0.44 (0; 0.82)	0.77 (0.64; 0.88)	4.6% (4.2%; 5.4%)	6% (5.6%; 6.4%)
Up to 12 months	33	7740	3903	3837	0.60 (0.43; 0.79)	47.62	(0.32; 1.10)	0.26 (0; 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	3163	1597	1566	0.66 (0.27; 1.23)	250	(0.11; 4.10)	0.77 (0; 1.55)	0.92 (0.75; 1.25)	6.1% (4.6%; 8.1%)	6.5% (5.7%; 7.7%)

CGs, control groups; CrI, credibility interval; IGs, intervention groups; *k*, number of studies/effects; NNT, number needed to treat; PI, prediction interval; s.m.d., standardised mean difference.
a. For effects on depressive symptom severity, NNTs were estimated using the method of Furukawa and Leucht[48], with control group event rates (CERs) imputed from reliable improvement rates in the CGs.
b. Calculated using regression standardisation (*G*-computation). Marginal risk ratios and their credible CrIs 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).
c. Defined as scoring PHQ-9 < 5. This analysis included only studies using PHQ-9, or some other instrument that could be converted to PHQ-9 scores using the common metric of Wahl et al.[24]

Table 3 Results of participant-level moderator analyses

Moderator	*k*	*N*	$\hat{\gamma}$ (95% CrI)	$\hat{\tau}$ (95% CrI)	$P(\lvert\gamma\rvert > 0)$
Depressive symptom severity	50	10 671	–0.09 (–0.14; –0.04)	0.08 (0.01; 0.15)	0.9998
Anxiety symptom severity	24	6229	–0.08 (–0.14; –0.02)	0.05 (0; 0.11)	0.9957
Relationship, yes	39	8677	–0.05 (–0.10; 0)	0.06 (0; 0.11)	0.9717
Previous psychotherapy, yes	10	2899	0.11 (–0.04; 0.27)	0.07 (0; 0.25)	0.9313
Sex, male	44	10 588	–0.04 (–0.09; 0.02)	0.08 (0; 0.14)	0.9226
Education, higher	36	9577	–0.02 (–0.07; 0.03)	0.06 (0; 0.13)	0.7920
Antidepressive medication, yes	17	5372	0.03 (–0.05; 0.11)	0.08 (0; 0.19)	0.7679
Chronic medical condition, yes	13	4677	0.02 (–0.07; 0.12)	0.07 (0; 0.17)	0.6966
Ethnicity, non-White	19	5370	0.02 (–0.08; 0.13)	0.13 (0; 0.24)	0.6529
Employment, yes	30	7786	0.01 (–0.05; 0.06)	0.04 (0; 0.11)	0.5929
History of MDD, yes	17	3515	–0.01 (–0.11; 0.08)	0.08 (0; 0.20)	0.5904
Age, years	49	10 437	–0 (–0.06; 0.05)	0.08 (0; 0.15)	0.5633

$\hat{\gamma}$, Standardised pooled coefficient of the treatment–covariate interaction; *k*, number of studies providing data; *N*, number of participants included in the analysis; $P(\lvert\gamma\rvert > 0)$, posterior tail probability of $\hat{\gamma}$ being greater/less than zero; MDD, major depressive disorder.

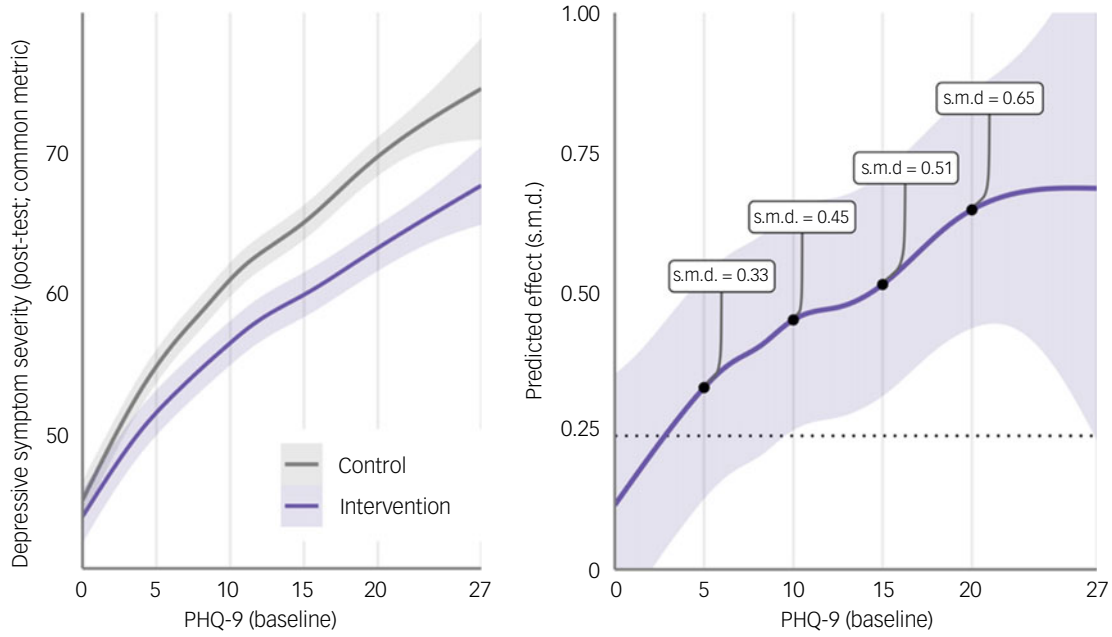

Fig. 2 Symptom severity and predicted treatment effects conditional on PHQ-9 baseline scores, based on a generalised additive mixed model with replicate cubic regression splines for both treatment groups ($K = 10$ basis functions). Models were fitted in the multiply imputed data and predictions obtained using the 'predict-then-combine'/pool-last approach. Analyses were restricted to studies including assessments of PHQ-9 at baseline, or instruments convertible to PHQ-9 as per the common metric of Wahl et al.[24] ($k = 47$, $N = 9598$). Signs of the predicted effect size were reversed, so that standardised mean difference (s.m.d.) values with a positive sign indicate favourable effects of the treatment. A population-level s.d. of 10 was assumed to standardise treatment effects, as implied by the common metric.[24]

interventions included in this IPD-MA already implement comparable methods.

Last, we also want to indicate 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 additional 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, including age, ethnicity, medical comorbidities, antidepressant use and past MDD episodes. If true, this would underline the broad applicability of psychological interventions across various subthreshold depression 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, not all putative moderators defined in our initial protocol could be analysed due to their absence in most, or all, studies. This includes variables such as traumatic events (at baseline or post-randomisation), childhood adversity, self-esteem and diet. We also only examined moderators individually, rather than 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. Third, while all trials allowed unrestricted access to usual care, uptake of other treatments was recorded in only a small subset and was therefore not analysed. While baseline co-interventions (i.e. antidepressant use) did not appear to moderate the treatment effect, future studies could prioritise the assessment of long-term treatment utilisation. This would help determine, for example, whether early intervention in

subthreshold depression influences future healthcare needs or how help-seeking behaviour relates to response and deterioration under usual care. Overall, such data would enable much more fine-grained longitudinal analyses of 'natural' recovery in subthreshold depression, which were not possible in this study. Last, we also note that 26% of our trials focused on older adults, and the mean age of our sample was therefore rather high ($M = 52.8$). This may restrict the generalisability of our findings to other populations. A more severe limitation is that only four studies (8%) were conducted in low- and middle-income countries (LMICs; China and Mexico). More evidence is needed to examine whether psychological interventions for subthreshold depression are equally effective in LMICs, where 80% of all people with mental disorders live.[47]

In sum, our findings support the routine provision of psychological interventions in individuals with subthreshold depression, 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 on how treatment benefits can be sustained over several years.

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Supplementary material

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Data availability

All extracted data are available in the manuscript and supplementary materials, as well as on the Metapsy website (docs.metapsy.org/databases/depression-psyctr). Individual-level data cannot be shared due to confidentiality agreements in the original studies. The corresponding author, M.H., may be contacted to determine whether specific data supporting our findings can be made available upon reasonable request. In most cases, data sharing will require a separate agreement between the requesting institution and the authors of the original studies for which data are requested.

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Author contributions

D.D.E. and P.C. conceived the study. C.B. further contributed to study design. C.B., M.H., A.A.S. and S.I. selected the studies and extracted data. M.C.A., S.M.A., E.A., O.P.A., J.B., K.M.P.v.B., P.J.B., H.B., V.S., R.B., R.J.C., D.C., H.C., M.C., L.C., J.C., K.S.D., E.D., S.G., B.L.H., R.H., K.H., M.R.I., E.K., N.K., J.P.K., C.K., K.I., M.A.L., H.-N.L., D.L., J.V.L., S.M., J.M.M., R.F.M., A.M., S.N., R.O., P.O., M.P.-O., A.M.P., C.F.R.III, B.W.R., J.P.S.-M., L.B.S., V.S., P.S., L.S., Y.T., F.L.V., I.V.-d.L., E.W., W.Y., S.Y.S.W., P.C., C.B. and D.D.E. contributed individual participant data. M.H., A.A.S. and S.I. verified the data. M.H. analysed the data. M.H., T.A.F., P.C., S.L. and C.B. interpreted the results. M.H. wrote the first draft of the manuscript. All authors had access to all the data, provided critical input and revisions to the draft manuscripts and approved the final manuscript. M.H., D.D.E. and C.B. had final responsibility for the decision to submit for publication.

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