Psychological interventions to prevent the onset of major depression in adults: a systematic review and individual participant data meta-analysis

Claudia Buntrock, Mathias Harrer, Antonia A Sprenger, Susan Illing, Masatsugu Sakata, Toshi A Furukawa, David D Ebert†, Pim Cuijpers*†, on behalf of the IPD-PrevDep Consortium‡*

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*Toshi Furukawa and Pim Cuijpers are retired

†Contributed equally as last authors

‡Members of the IPD-PrevDep Consortium are listed at the end of this Article

Institute of Social Medicine and Health Systems Research, Medical Faculty, Otto-von-Guericke-University Magdeburg, Magdeburg, Germany (C Buntrock PhD, A A Sprenger MSc); **Psychology and Digital Mental Health Care Research Unit, School of Medicine and Health, Technical University of Munich, Munich, Germany** (M Harrer MSc, S Illing BA, D D Ebert PhD); **Department of Neurodevelopmental Disorders, Nagoya City University, Nagoya, Japan** (M Sakata PhD); **Department of Health Promotion and Human Behavior, Kyoto University Graduate School of Medicine and School of Public Health, Kyoto, Japan** (M Sakata); **Kyoto University Office of Institutional Advancement and Communications, Kyoto, Japan** (Prof T A Furukawa PhD); **Department of Clinical Neuro- and Developmental Psychology, VU University Amsterdam, Amsterdam, Netherlands** (Prof P Cuijpers PhD)

Correspondence to: Dr Claudia Buntrock, Institute of Social Medicine and Health Systems Research, Medical Faculty, Otto-von-Guericke-University Magdeburg, 39120 Magdeburg, Germany **claudia.buntrock@med.ovgu.de**

Summary

Background Psychological interventions are increasingly discussed as a method to prevent major depressive disorder (MDD) in adults who already experience subthreshold depressive symptoms. In this individual participant data meta-analysis, we quantify the effect of preventive interventions against control on MDD onset in this population, and explore effect modifiers.

Methods In this systematic review and individual participant data meta-analysis, we screened full-texts of eligible studies within the Metapsy research domain for articles on psychological interventions for depression, from database inception to May 1, 2023, published in English, German, Spanish, and Dutch. We included individual participant data of randomised trials comparing psychological interventions with a control group regarding their effects on MDD onset in adults with subthreshold depressive symptoms but no MDD at baseline, confirmed by standardised diagnostic interviews. Risk of bias was assessed using the RoB 2 tool. Effect on the onset of MDD (the primary outcome) and moderators were analysed using one-stage individual participant data meta-analysis. Survival analyses were conducted to examine effects on time to MDD onset within 12 months. We involved people with related lived experience in the study design and implementation. This study is registered with PROSPERO, CRD42017058585.

Findings 30 of 42 eligible randomised controlled trials with 7201 participants (2227 [30·9%] male, 4957 [68·9%] female, and 17 [0·2%] preferred not to report their sex) were included in our analysis (3697 participants had intervention and 3504 participants had control). The mean age of participants was 49·9 years (SD 19·2). Of the 3152 participants with reported ethnicity, 1608 (51·0%) were White. Five studies received a high risk of bias rating. Psychological interventions were associated with significantly reduced MDD incidence at post-treatment (incidence rate ratio [IRR] 0·57 [95% CI 0·35–0·93]; τ^2=0·29; 18 studies), within 6 months (0·58 [0·39–0·88]; τ^2=0·11; 18 studies), and within 12 months (0·67 [0·51–0·88]; τ^2=0·05; 19 studies). No significant effect was observed at 24 months (IRR 1·16 [95% CI 0·66–2·03]; τ^2=0·10; six studies). Preventive effects were stronger for individuals who had not previously had psychotherapy (IRR 0·39 [95% CI 0·25–0·62]) compared with those who had received psychotherapy before (0·92 [0·61–1·36]; p=0·029; seven studies). Although no overall linear association was identified, higher baseline depressive (Patient Health Questionnaire-9) and anxiety symptom (Generalized Anxiety Disorder-7) scores were associated with greater reductions in MDD onset risk. On the study level, delivery type appeared to moderate outcomes, with conference telephone calls being more effective than delivery via face-to-face, internet-based, and other formats (p=0·002), albeit based on only two studies of conference telephone calls with four comparisons. Other factors (eg, age) showed no significant differential effects.

Interpretation Our findings show the effectiveness of preventive psychological interventions for subthreshold depressive symptoms. Tailoring interventions to consider participant-level and study-level factors could help to increase the impact of such interventions on a population level.

Funding None.

Introduction

Major depressive disorder (MDD) ranks among the most prevalent mental health conditions globally,[1] and its worldwide prevalence has increased in the past 20 years.[2] MDD accounts for 7·5% of all years lived with disability,[3] and imposes a substantial economic burden on society, estimated at US$326·2 billion annually in the USA alone.[4]

Despite the availability of effective first-line treatments for MDD, including pharmacotherapy, psychotherapy, and digital interventions (eg, programme delivered via the web or mobile applications), their impact in adults is

Research in context

Evidence before this study

We searched the National Library of Medicine via PubMed, from database inception to May 1, 2024, for peer-reviewed publications in English using the search string ("depression"[MeSH Terms] OR "depressive disorder"[MeSH Terms]) AND ("prevention"[Title] OR "preventing"[Title] OR "prevent"[Title] OR "subthreshold"[Title] OR "subclinical"[Title]) AND ("psychological"[Title/Abstract] OR "intervention"[Title/Abstract]) AND "meta-analysis"[Title]. We identified 68 records, of which five were systematic reviews with meta-analyses that, based on title and abstract, were eligible to report on the effects of psychological interventions for depression prevention outcomes (eg, odds ratio, relative risk, or hazard ratio). Although these studies evaluated the effects of various psychological interventions on the onset of major depressive disorder (MDD), only one study used an individual participant data meta-analysis to explore effect modifiers related to depressive symptom severity, rather than MDD onset. This analysis was restricted to internet-based interventions. As a result, there was a scarcity of evidence from previous research on effect modifiers for different types of psychological interventions on MDD onset.

Added value of this study

To our knowledge, this is the first systematic review and individual participant data meta-analysis to identify effect modifiers of different types of psychological interventions on MDD onset at both the individual level and study level. We included data from 30 trials with 7201 participants. Our individual participant data meta-analysis showed that psychological interventions significantly reduced the incidence of MDD at post-treatment and within 6 months and 12 months after the intervention. However, the effect waned by the 24-month follow-up. Furthermore, we found that no previous psychotherapy experience resulted in greater effects in preventing MDD. Individual characteristics, such as higher baseline depressive (Patient Health Questionnaire-9 ≥10) or anxiety symptoms (Generalised Anxiety Disorder-7 ≥10), appeared to be associated with stronger preventive effects. Conference telephone calls, although assessed in only two studies, appeared more effective than face-to-face, internet-based, or other formats.

Implications of all the available evidence

Psychological interventions have the potential to prevent MDD onset in individuals not currently experiencing a depressive episode. Further investigations are needed to determine the threshold at which depressive symptoms, at the lower end of the severity spectrum, become persistent enough to warrant preventive interventions. Future research and policy efforts should prioritise strategies to integrate these interventions into routine care settings, addressing the current implementation gap.

modest.[5,6] A modelling study suggests that even with optimal coverage of evidence-based treatments, the overall disease burden of MDD can only be reduced by one-third.[7] Similarly, real-world evidence indicates that only about 16·5% of patients with depression, even in high-income countries, receive minimally adequate treatment.[8]

Effective prevention approaches, with the potential to mitigate initial episodes and decrease recurrent episodes of MDD, are needed to reduce the overall prevalence of MDD.[9] Indicated prevention, targeting individuals already exhibiting subthreshold symptoms of depression, has garnered particular attention. This focus is driven by the estimated 11% prevalence rate of subthreshold symptoms of depression in the general population,[10] coupled with its comparable adverse effects on quality of life as MDD.[11] Notably, individuals with subthreshold symptoms of depression have about a three-times greater risk of developing MDD compared with individuals without symptoms of depression.[10]

Psychological interventions reduce the relative incidence of MDD in adults by 19% within a year, but a notable proportion of participants still develop MDD.[12] Advancements in prevention efforts can be made by identifying participant characteristics to refine and personalise interventions, improving outcomes for individuals with subthreshold depression symptoms. However, existing evidence is conflicting; a systematic review found moderate evidence that effectiveness of psychological interventions for depression prevention increased as participants' age decreased.[13] By contrast, an individual participant data meta-analysis[14] examined internet-based preventive interventions for subthreshold depressive symptoms and found that the effects on symptom severity became more pronounced with increasing age. In addition, the effectiveness of these interventions increased with the severity of the initial depressive symptoms.[14] However, this analysis did not assess effect modifiers for MDD onset and included only seven studies, limiting its generalisability beyond internet interventions. Our study aimed to investigate the effects of various psychological interventions versus control conditions on both MDD onset and symptom severity in adults with subthreshold depressive symptoms assessed in randomised controlled trials, while assessing effect modifiers for MDD onset at both participant and study levels.

Methods

Search strategy and selection criteria

This systematic review and individual participant data meta-analysis is registered with PROSPERO, CRD42017058585). Analyses are reported according to the Preferred Reporting Items for Systematic Review and

See Online for appendix

Meta-Analyses of individual participant data statement (appendix pp 1–4).[15] The rationale and methods of this study are described in greater detail in a published protocol.[16] Deviations from the planned approach are reported in the appendix (p 5). Ethical approval and participant consent were obtained within the context of the primary studies. We involved people with related lived experience in the study design and implementation.

In this individual participant data meta-analysis, we included randomised trials in which a psychological intervention was compared with a comparison group (waitlist, care as usual, placebo, or antidepressant medication) with regard to effects on MDD onset (ie, the incidence of new episodes of MDD during the study period as confirmed by a standardised diagnostic interview), in adults aged 18 years and older with subthreshold depressive symptoms but no MDD at baseline, as confirmed by a standardised diagnostic interview. Studies that met the eligibility criteria outlined in the study protocol but used self-report measures instead of diagnostic interviews during follow-up were excluded, as they did not provide data on the primary outcome (ie, onset of MDD). Having subthreshold symptoms of depression was defined as scoring higher than a cutoff score on a self-rating depression questionnaire; scoring higher than a cutoff score on a clinician-rated instrument; or meeting criteria for minor depression according to the DSM-IV, or the ICD. Psychological intervention was defined as the "application of psychological mechanisms and interpersonal stances derived from psychological principles for the purpose of assisting people to modify their behaviours, cognitions, emotions and/or other personal characteristics in directions that the participants deem desirable".[16]

In studies without an elevated depressive symptom threshold for inclusion, only participants with at least mild depressive symptoms at baseline (Patient Health Questionnaire [PHQ]-9 score ≥5) were included. Scores from other symptom questionnaires were converted to PHQ-9 values using a common metric.[17]

For more on **psychological interventions for depression from Metapsy** see https://docs.metapsy.org/databases/depression-psyctr/

To identify eligible studies, two independent researchers screened the full texts of the Metapsy database on psychological interventions for depression. The Metapsy database includes articles in English, German, Spanish, and Dutch. Disagreements were resolved by a senior researcher. The database is updated three times a year through systematic searches of PubMed, Embase, PsycINFO, and Cochrane Central. Full search strings are provided in the appendix (pp 6–9). In each update, two independent researchers screened titles, abstracts, and full texts of eligible studies, resolving disagreements by consensus. Additionally, previous systematic reviews and meta-analyses on MDD prevention were reviewed, and experts were consulted for other relevant studies. Studies published up to May 1, 2023, were included.

Corresponding authors of all eligible articles were contacted to request permission to use their data, with reminders sent after 2 weeks and 1 month. If there was no response, the trial was excluded. Responding authors provided data on demographic, clinical, outcome, and intervention-related characteristics, with variables selected based on a pre-defined list of predictors of long-term outcomes in depression (appendix p 10).[16] Data were collated centrally by independent researchers (MH, AS, and SI), and cross-checked with the trial publications. Depressive symptom severity measures were transformed into a common metric using a partial credit model to facilitate joint analyses.[17] The harmonised individual participant data were merged into a single dataset after a standardised protocol. Post-intervention assessments were treated as one assessment point, and follow-ups were categorised by length (up to 6 months, 12 months, or 24 months). For studies that did not provide individual participant data, suitable outcome data (ie, number of participants with and without MDD at any given timepoint after intervention), were extracted for a conventional aggregate data meta-analysis if available in the published report.

Risk of bias was planned to be assessed using version 1 of the Cochrane risk of bias (RoB) tool. An updated version of the tool (RoB 2[18]) has been released and was used to assess the randomisation process, deviation from the intervention, missing outcome data, measurement of the outcome, and selection of the reported results. All studies were rated as being at low risk of bias for missing outcome data, since multiple imputation with auxiliary variables could be used to handle missing data consistently in this individual participant data meta-analysis, and missingness at random was assumed to be plausible.

Outcomes

The primary outcome was the onset of a MDD (first or recurrent episode). MDD cases after treatment and during follow-up (up to 6 months, 12 months, and 24 months) had to be confirmed using clinical interviews. Additionally, we examined effects on time to MDD onset. Secondary outcomes were depressive symptom severity (transformed into common metrics), 50% symptom reduction compared with baseline, near symptom-free status (defined as scores equivalent to PHQ-9 <5[19]), as well as reliable improvement and reliable deterioration in depressive symptoms, which were determined using the reliable change index (RCI). We did not include quality of life, anxiety, or suicidal thoughts and behaviour as secondary outcomes due to insufficient available data.

Data analysis

All analyses followed the intention-to-treat principle. Missing data were handled using multiple imputation (fully conditional specification; MICE algorithm) under the missing at random assumption. Multilevel two-stage imputation models with heteroscedastic errors were used to account for the nested data structure[20] (appendix p 11).

Highly collinear variables and variables with systematically missing information (structural zeros) were excluded as predictors. A total of m=50 imputation sets were generated. For moderator analyses, substantive model compatible fully conditional specification was used separately for each study and putative moderator.[21] These models included a treatment-covariate interaction with the examined moderator variable as well as auxiliary variables.

Using one-stage individual participant data meta-analysis, we calculated pooled effects on MDD onset, depressive symptom severity, 50% symptom reduction, near symptom-free status, reliable improvement and reliable deterioration (according to RCI) at post-treatment and follow-up (ie, up to 6 months, 12 months, and 24 months). Generalised linear mixed models were used for all analyses. Poisson models were used for MDD onset, with the study-specific observation period serving as an offset. A normal linear model with stratified trial intercepts and trial-specific error terms was used for depressive symptom severity, and a binomial logit-link model was used for the other outcomes. All models were adjusted for baseline symptom severity, centred around trial means, and fitted in the multiply imputed data, with final estimates aggregated using Rubin's rules. Marginal incidence rate ratios (IRRs) and relative risk (RR) estimates were obtained using G-computation,[22] and standardised mean differences were calculated for depressive symptom severity using the pooled endpoint SD. Number-needed-to-treat values were derived from standardised mean differences[23] with the control group event rate obtained from the individual participant data. We used I^2 to quantify the between-study heterogeneity (appendix p 11). As a sensitivity analysis, we also used two-stage individual participant data meta-analysis models with a log-normal model and a continuity correction of 0·5, using the restricted maximum likelihood estimator for the between-study heterogeneity variance τ^2. Conventional meta-analyses, including studies without individual participant data, were also conducted for MDD onset and depressive symptom severity, with subgroup analyses comparing studies that provided data with those that did not. Survival analysis was conducted for time to MDD onset (expressed in weeks). The Kaplan–Meier estimator was used to calculate survival functions by treatment status within a 12-month study period. MDD-free participants were censored at the time of study termination or loss to follow-up, whichever occurred first. Non-informative censoring was assumed. Mixed-effects Cox regression models with stratified trial intercepts were fitted to estimate the pooled treatment effect on time to MDD onset. Hazard ratios (HRs) and 95% CIs were derived based on the model's estimated intervention effect. We evaluated the proportional hazards assumption by examining the scaled Schoenfeld residuals. We used a delta-adjustment approach to control for the possibility that data are missing not at random. Data were imputed under the assumption that, in each trial, the incidence of MDD among participants lost to follow-up who had received the intervention was 5% to 30% higher than predicted by the main imputation model.

We examined moderators of the effect on MDD onset by including treatment-covariate interaction terms (including main effects) into the Poisson model. Moderator analyses were only conducted for MDD onset at the first available assessment. As putative effect modifiers on participant level, sex, age, ethnicity, education, employment status, relationship status, baseline depressive symptom severity (PHQ-9) and anxiety symptom severity (Generalized Anxiety Disorder [GAD]-7), presence of chronic medical conditions, history of MDD, intake of anti-depressive medication, and previous psychotherapy were explored. After identifying eligible studies, we screened the articles for prespecified effect modifiers and included only those for which we expected to obtain sufficient data. We used continuous variables in their original form to preserve the full range of information, as dichotomising or categorising them can lead to a loss of statistical power and precision. However, in some instances, variables were dichotomised to simplify the analysis, necessitated by inconsistencies in data collection across studies. As study-level variables, we examined if the country of origin, publication year, type of delivery, intervention type, type of control condition, or risk of bias predicted differential intervention effects. For significant continuous moderators, we also estimated the conditional treatment effects on MDD incidence at representative values of the covariate (ie, psychometrically validated cut-off scores). Analyses were conducted using R (version 4.2.0).

Role of the funding source

There was no funding source for this study.

Results

Of 1013 full-text articles screened, 42 were determined to be eligible for this study figure 1. Individual participant data could be obtained from 30 (71·43%) of all eligible trials. No major issues were identified during the assessment of individual participant data. Of the studies from which no individual participant data could be obtained, aggregate data were available for ten studies. This finding corresponds to 1190 additional participants (599 with intervention and 591 with control) who were eligible for combined analysis of individual participant data and aggregate data. References of the included studies are provided in the appendix (pp 12–15).

Study characteristics are summarised in the appendix (pp 16–30). 26 studies (86·7%) were conducted in high-income countries, nine (30·0%) in general adult populations, nine (30·0%) in older adults (with two studies conducted in nursing home residents), three (10·0%) in pregnant women, four (13·3%) in university students, three (10·0%) in non-professional caregivers, one (3·3%) in employees, and one (3·3%) in patients with diabetes. Most interventions were based on cognitive behavioural therapy (16 [53·3%] studies) and

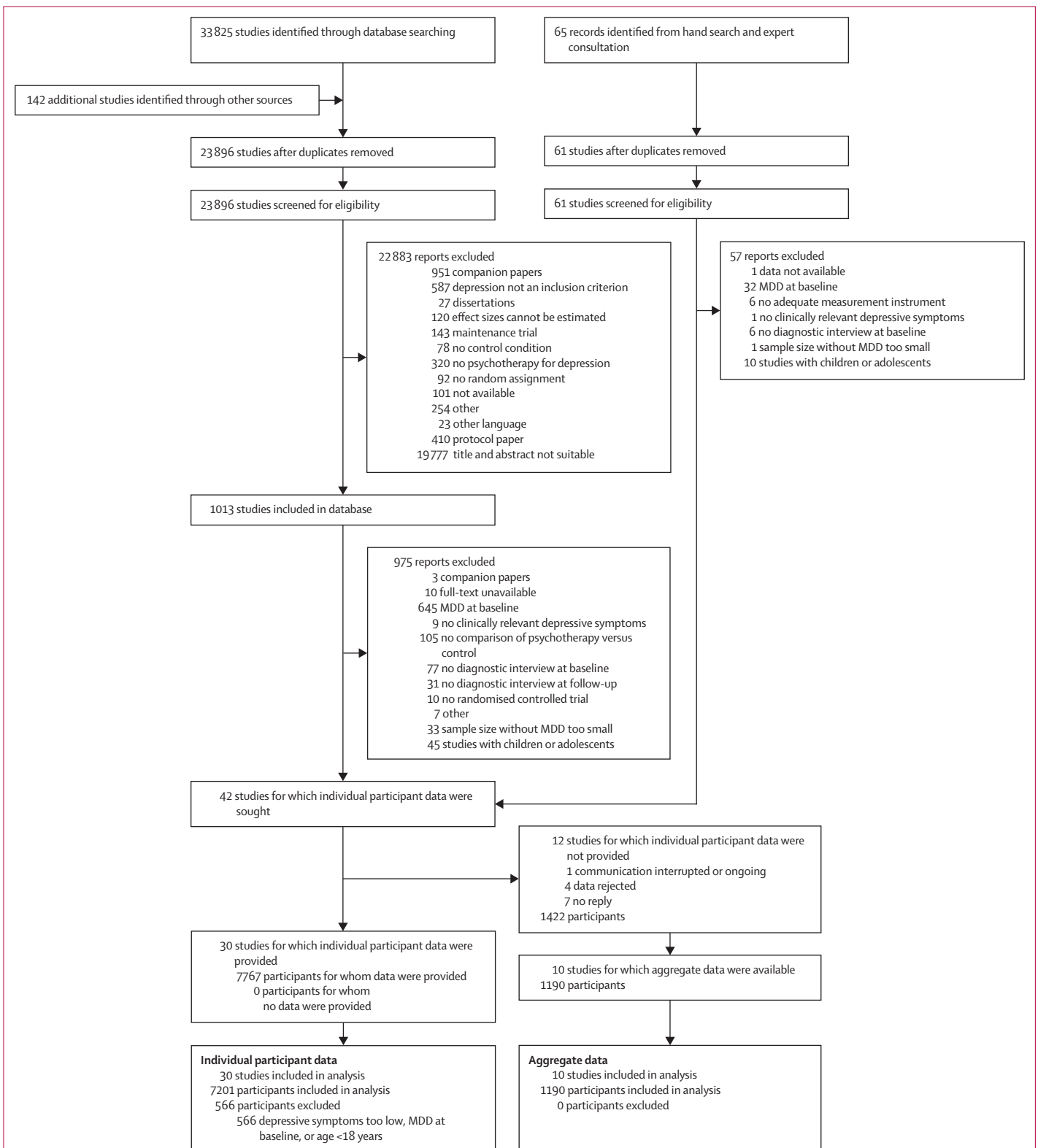


Figure 1: **Study selection**
MDD=major depressive disorder.

were provided in a face-to-face format (12 [40·0%] studies). We included 7201 participants (3697 with intervention and 3504 with control) with a mean age of 49·9 years (SD 19·2). Of the participants, 2227 (30·9%) were male, 4957 (68·9%) female, and 17 (0·2%) preferred not to record their sex. Of the 3152 participants with reported ethnicity, 1608 (51·0%) were White. Of the 6605 participants who reported their educational level, 3305 (50·0%) had a higher education. Participant characteristics at baseline are provided in the appendix (p 31).

Risk of bias assessments for each included study are displayed in the appendix (pp 16–22). The overall risk of bias was low. With one exception, all studies used an adequate sequence generation mechanism (domain 1) and showed low risk of bias due to deviations from the intended interventions (domain 2). An intention-to-treat analysis could be performed in all trials (domain 3).

	Effect size (95% CI)*	Number of studies	τ^2	I^2	*t*	ν	*p*†	FMI	NNT (95% CI)	Event rate	
										Control*	Intervention*
MDD incidence (incidence rate ratio)											
Post-treatment	0·57 (0·35 to 0·93)	18	0·292	40·8%	–2·588	872·8	0·010	0·239	19·93 (8·72 to 69·87)	15·0% (3·7 to 26·3)	10·0% (0·8 to 19·3)
Up to 6 months follow-up	0·58 (0·39 to 0·88)	18	0·110	21·6%	–2·340	258·5	0·020	0·440	37·81 (18·43 to 728·83)	8·7% (3·3 to 14·2)	6·1% (0·6 to 11·6)
Up to 12 months follow-up	0·67 (0·51 to 0·88)	19	0·052	16·3%	–2·954	872·0	0·003	0·239	20·54 (11·74 to 82·09)	14·0% (8·1 to 19·9)	9·1% (5·0 to 13·2)
Up to 24 months follow-up	1·16 (0·66 to 2·03)	6	0·098	19·4%	0·398	6337·7	0·691	0·088	388·52 (23·39 to 20·88)	7·7% (2·4 to 13·0)	7·9% (3·8 to 12·1)
Symptom severity, g											
Post-treatment	–0·49 (–0·66 to –0·32)	28	0·176	90·5%	–5·572	20 988·4	<0·001	0·048	7·00 (4·88 to 11·57)	–	–
Up to 6 months follow-up	–0·26 (–0·41 to –0·11)	23	0·082	82·3%	–3·412	1455·1	0·001	0·185	20·68 (12·01 to 53·49)	–	–
Up to 12 months follow-up	–0·27 (–0·40 to –0·14)	23	0·077	79·4%	–4·027	38 377·9	<0·001	0·036	14·39 (9·12 to 29·90)	–	–
Up to 24 months follow-up	–0·14 (–0·32 to 0·04)	11	0·055	66·9%	–1·523	2985·4	0·128	0·129	44·30 (17·15 to 165·32)	–	–
50% symptom reduction (RR)											
Post-treatment	1·86 (1·43 to 2·41)	28	0·772	89·4%	5·225	27 127·9	<0·001	0·043	5·19 (8·48 to 3·74)	24·5% (18·9 to 30·1)	43·8% (37·3 to 50·3)
Up to 6 months follow-up	1·47 (1·23 to 1·75)	23	0·266	79·1%	4·109	1816·4	<0·001	0·165	7·45 (13·32 to 5·17)	31·1% (25·5 to 36·8)	44·6% (38·0 to 51·1)
Up to 12 months follow-up	1·37 (1·17 to 1·60)	23	0·254	78·6%	3·757	13 590·3	<0·001	0·060	8·31 (15·98 to 5·62)	36·0% (30·2 to 41·9)	48·1% (42·7 to 53·4)
Up to 24 months follow-up	1·27 (1·04 to 1·54)	11	0·193	74·1%	1·059	4776·3	0·290	0·102	9·71 (51·98 to 5·36)	45·1% (35·3 to 54·9)	55·4% (47·1 to 63·7)
Near symptom-free status (RR)											
Post-treatment	1·71 (1·33 to 2·20)	28	0·930	94·5%	4·506	35 615·8	<0·001	0·037	5·96 (10·73 to 4·13)	34·3% (27·2 to 41·3)	51·0% (45·1 to 57·0)
Up to 6 months follow-up	1·34 (1·13 to 1·59)	23	0·404	90·4%	3·020	4361·1	0·003	0·106	9·02 (20·73 to 5·77)	41·7% (34·9 to 48·6)	52·8% (45·8 to 59·8)
Up to 12 months follow-up	1·32 (1·12 to 1·55)	23	0·431	88·2%	3·141	42 319·5	0·002	0·034	9·09 (21·31 to 5·78)	45·9% (38·7 to 53·2)	56·9% (50·7 to 63·2)
Up to 24 months follow-up	1·23 (1·03 to 1·48)	11	0·241	81·3%	1·226	2730·9	0·220	0·135	9·12 (37·21 to 5·19)	56·9% (43·2 to 70·7)	67·9% (57·6 to 78·2)
Reliable improvement (RR)											
Post-treatment	1·72 (1·38 to 2·14)	28	0·850	91·2%	5·282	49 702·5	<0·001	0·031	5·37 (8·89 to 3·85)	30·7% (25·9 to 35·4)	49·3% (41·3 to 57·4)
Up to 6 months follow-up	1·46 (1·26 to 1·70)	23	0·192	73·7%	5·023	1891·7	<0·001	0·162	8·01 (12·83 to 5·83)	35·3% (29·7 to 40·9)	47·8% (41·4 to 54·1)
Up to 12 months follow-up	1·42 (1·26 to 1·61)	23	0·120	65·2%	5·721	4351·7	<0·001	0·107	8·10 (12·18 to 6·06)	38·2% (32·9 to 43·5)	50·5% (44·5 to 56·6)
Up to 24 months follow-up	1·33 (1·07 to 1·67)	11	0·234	77·4%	1·645	4178·1	0·100	0·109	10·41 (40·87 to 5·96)	42·5% (34·3 to 50·7)	52·1% (43·7 to 60·4)

(Table 1 continues on next page)

	Effect size (95% CI)*	Number of studies	τ^2	I^2	*t*	ν	*p*†	FMI	NNT (95% CI)	Event rate	
										Control*	Intervention*
(Continued from previous page)											
Reliable deterioration (RR)											
Post-treatment	0·48 (0·36 to 0·63)	28	0·152	32·5%	–5·222	1987·1	<0·001	0·158	18·46 (13·17 to 30·87)	11·2% (8·9 to 13·5)	5·8% (3·9 to 7·7)
Up to 6 months follow-up	0·65 (0·50 to 0·86)	23	0·163	39·8%	–2·632	1368·2	0·009	0·190	38·79 (21·28 to 219·09)	10·5% (8·1 to 12·8)	7·9% (4·7 to 11·0)
Up to 12 months follow-up	0·59 (0·46 to 0·76)	23	0·029	8·8%	–4·135	686·2	<0·001	0·269	27·30 (18·70 to 50·59)	9·8% (7·5 to 12·1)	6·1% (4·3 to 8·0)
Up to 24 months follow-up	0·59 (0·34 to 1·03)	11	0·432	53·1%	–1·366	2216·1	0·172	0·149	23·20 (11·00 to 212·02)	10·3% (4·8 to 15·8)	6·0% (3·1 to 8·8)

FMI=fraction of missing information due to non-response. MDD=major depressive disorder. NNT=number needed to treat. RR=risk ratio. τ^2=between-study heterogeneity variance. I^2=between-study heterogeneity. ν=degrees of freedom (multiple imputation large-sample approximation by Rubin, 1987, equation 3.1.6). *Calculated using regression standardisation (*G*-computation). CIs around these marginal effect estimates are generated using the delta method and can diverge in their interpretation of significance from the *t*-test of the intervention effect as measured by the treatment indicator coefficient. †Test of the treatment indicator coefficient (one-stage individual participant data meta-analysis model)

Table 1: **Pooled effects on MDD incidence, symptom severity, response, and reliable deterioration**

Four (13·3%) studies showed high risk of bias in measurement of the outcome (domain 4). With one exception, all studies had a low risk for selective reporting (domain 5).

Proportions of missing outcome data are provided in the appendix (pp 32–34). An overview of results is presented in table 1. We found that psychological interventions reduced the incidence of major depression after treatment (IRR 0·57 [95% CI 0·35–0·93]; 18 studies), within 6 months (0·58 [0·39–0·88]; 18 studies), and within 12 months (0·67 [0·51–0·88]; 19 studies). This finding means that interventions reduced the incidence of depression by 43%, 42%, and 33%, respectively, compared with control. The few studies which recorded the incidence of depression up to 24 months did not yield a significant pooled effect (IRR 1·16 [95% CI 0·66–2·03]; six studies). A forest plot detailing the results on depression incidence is provided in figure 2.

Similar findings emerged for all other outcomes. At post-treatment (n=28 studies), within 6 months (23 studies), and within 12 months (23 studies), we found that interventions led to a reduction in depressive symptom severity (standardised mean difference –0·49 [95% CI–0·66 to –0·32] to –0·26 [–0·41 to –0·11]), an increase in the number of participants with 50% symptom reduction (RR 1·37 [95% CI 1·17–1·60] to 1·86 [1·43–2·41]), symptom-free status (1·32 [1·12–1·55] to 1·71 [1·33–2·20]), and reliable improvement (1·42 [1·26–1·61] to 1·72 [1·38–2·14]), as well as a decrease in reliable symptom deterioration (0·48 [0·36–0·63] to 0·65 [0·50–0·86]), compared with controls. No significant effects were observed at 24-month follow-up (all p≥0·05; 11 studies). Between-study heterogeneity was moderate to high in most analyses (I^2 range 19·4% to 94·5%; table 1).

Analyses using two-stage models closely mirrored the main findings (appendix p 35). Results from combined analyses of individual participant data and aggregate data studies showed largely similar effect estimates, for both for MDD onset and depressive symptom severity (appendix p 36). The effect on depression incidence up to 24 months was not significant (IRR 0·83 [95% CI 0·61 to 1·13]; eight studies). Effects of studies that provided individual participant data did not differ significantly from those of studies that did not for all analysed assessment points and outcomes (all p>0·05). Effects on 12-month incidence remained robust under all examined missing-not-at-random scenarios. At post-test and up to 6 months, effects remained significant under minor deviations from missingness at random (appendix pp 37–38).

Eight (26·7%) of the 30 studies provided time to MDD onset data suitable for a pooled survival analysis (2670 participants; 1337 with intervention and 1333 with control). In the intervention groups, 227 (17·0%) participants experienced MDD onset during the study period, compared with 301 (22·6%) in the control groups. Kaplan–Meier survival curves for the intervention and control groups across all trials are presented in figure 3. The 6-month incidence rate of MDD onset was 13·4% (95% CI 11·5–15·6) in the intervention groups versus 17·9% (15·8–20·3) in the control groups; whereas the 12-month incidence rate in the intervention groups was 21·4% (19·1–24·1) compared with 27·4% (24·8–30·2) in the control groups. Using mixed-effects Cox regression controlling for baseline depressive symptom severity, the pooled preventive effect of the interventions was estimated at an HR of 0·76 (95% CI 0·64–0·90). This effect was significant (p<0·001) and means that, given individuals with the same initial depressive symptom severity, provision of the intervention reduces the hazard of MDD onset within 12 months by 24%.

On a participant level, individuals who had not previously undergone psychotherapy showed stronger preventive effects against MDD onset than individuals

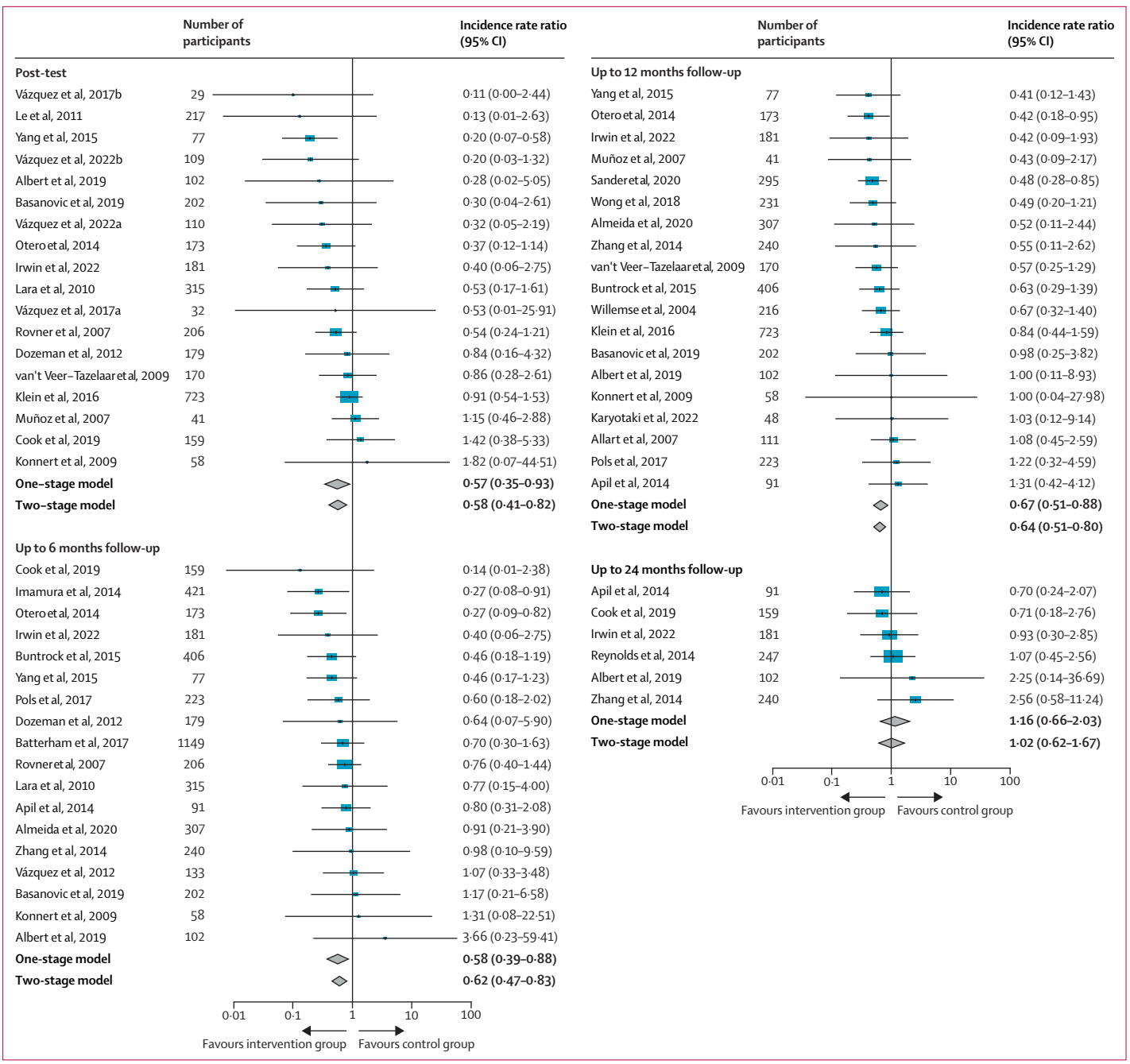
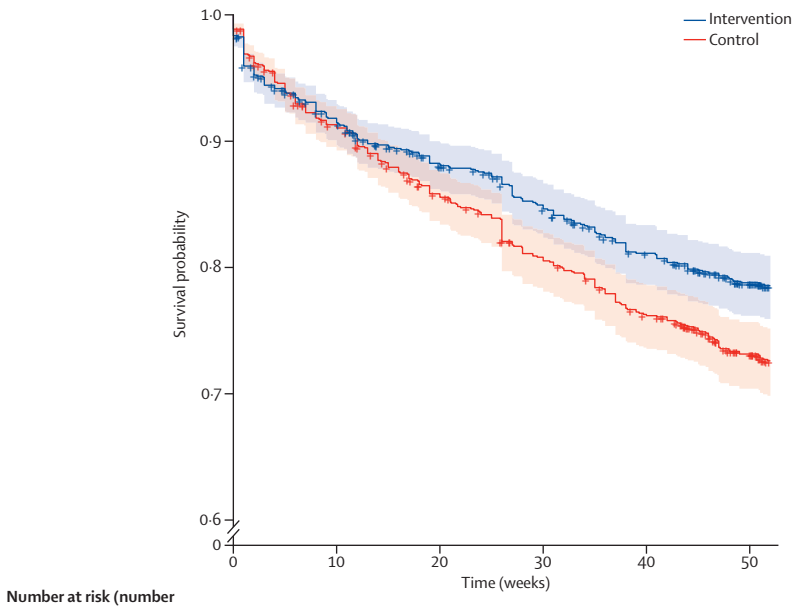


Figure 2: **Forest plot for effects on MDD onset at post-treatment and up to 6 months, 12 months, and 24 months**
Vázquez et al, 2017a and Vázquez et al, 2020a compared behavioural activation and control. Vázquez et al, 2017b and Vázquez et al, 2020b compared cognitive behavioural therapy and control. Full details of all included studies are in the appendix (pp 16–22).

who had received psychotherapy before (seven studies, e^{β} 2·292 [SE 0·38], p=0·029). A marginal IRR of 0·92 (95% CI 0·61–1·36) was computed for patients with psychotherapy experience, compared with an IRR of 0·39 (95% CI 0·25–0·62) for those without. No moderator effects were found for sex, age, ethnicity, education, employment, relationship status, chronic medical conditions, MDD history, or antidepressant use.

No significant linear relationship was found between baseline depressive symptom severity and effects on MDD onset (30 studies; e^{β} 1·016 [SE 0·128]; p=0·900; table 2). However, estimated marginal intervention effects appeared stronger for higher baseline PHQ-9 scores: IRR 0·72 (95% CI 0·53–0·99) at a score of 5 (mild depressive symptoms), 0·56 (0·41–0·76) at score 10 (moderate depressive symptoms), and 0·59 (0·45–0·78)



Number at risk (number censored)						
Control	1333 (162)	1053 (177)	937 (232)	840 (275)	788 (280)	698 (339)
Intervention	1337 (207)	1014 (228)	907 (299)	831 (340)	779 (356)	714 (402)

Figure 3: **Time to depression onset**
The mean duration of the interventions was 13·3 weeks (range 2–52 weeks).

	Number of studies	β	√v̂(β)	τ^2 (95% CI)	*t*	p value
Depressive symptom severity	30	0·016	0·128	0·253 (0·000–1·017)	0·126	0·900
Anxiety symptom severity	10	–0·195	0·260	0·403 (0·000–1·425)	–0·837	0·402
Sex, male	25	0·073	0·242	0·000 (0·000–0·000)	0·293	0·770
Age, years	30	0·129	0·116	0·195 (0·000–0·731)	1·046	0·296
Ethnicity, non-White	8	0·726	0·532	0·000 (0·000–2·519)	1·027	0·304
Education, higher	21	0·196	0·270	0·000 (0·000–0·100)	0·663	0·507
Employment, yes	16	–0·037	0·293	0·000 (0·000–1·014)	–0·130	0·897
Relationship, yes	27	–0·105	0·233	0·000 (0·000–0·908)	–0·475	0·635
Chronic medical condition, yes	10	0·013	0·585	0·000 (0·000–0·853)	0·022	0·982
History of MDD, yes	11	0·020	0·442	0·000 (0·000–0·450)	0·045	0·964
Antidepressive medication, yes	8	–0·103	0·366	0·000 (0·000–1·250)	–0·296	0·767
Previous psychotherapy, yes	7	0·829	0·381	0·000 (0·000–1·499)	2·179	0·029

MDD=major depressive disorder.

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

at score 15 (moderately severe depressive symptoms). Similarly, higher baseline GAD-7 scores were associated with stronger effects: IRR 0·71 (95% CI 0·42–1·21) at score 5, 0·59 (0·36–0·98) at score 10, and 0·52 (0·30–0·91) at score 15. On a study level, delivery type significantly affected preventive effects (interaction p=0·002), with conference telephone calls (IRR 0·24 [95% CI 0·11–0·53]) being potentially more effective than other methods (IRR 0·63–0·71), although based on a small sample (two studies with four comparisons). Geographical region, intervention type, publication year, control condition, and risk of bias showed no significant differences in preventing MDD onset (table 3).

Discussion

This systematic review and individual participant data meta-analysis synthesised data from 30 randomised controlled trials with 7201 participants, mostly from high-income countries. The overall study quality was satisfactory, although five studies had a high risk of bias. Psychological interventions showed strong evidence of positive outcomes up to 12 months, including reduced MDD incidence, depressive symptom severity, increased proportions of participants with 50% symptom reduction, near symptom-free status, and reliable improvement, along with decreased reliable symptom deterioration. Psychological interventions were more effective in preventing MDD onset in individuals without previous psychotherapy experience and appeared more effective in those with initial moderate to moderately severe depressive or anxiety symptoms (PHQ-9 or GAD-7 ≥10), indicated by smaller IRRs. However, the overlapping CIs and non-significant interaction term warrant caution in interpreting this result.

Our findings support previous individual participant data meta-analysis findings that highlight the potential of psychological interventions to prevent MDD onset in individuals not currently experiencing a depressive episode. Our one-stage individual participant data meta-analysis showed a significantly reduced incidence of depression by 42% up to 6 months, which was maintained with a 33% reduction up to 12 months. This finding exceeds the results of previous conventional meta-analyses by Cuijpers and colleagues[12] (19% reduction) and Huang and colleagues[24] (22% reduction). Individual participant data meta-analyses examine individual-level data, accounting for variability and potential biases, providing more precise estimates of intervention effects. Our results align with an individual participant data meta-analysis of internet-based interventions[14] and meta-analyses of online psychological and psychoeducational interventions,[25] and self-guided internet interventions.[26] However, the two meta-analyses[25,26] did not require diagnostic interviews at baseline for assessing depression diagnosis. The secondary outcome findings from our individual participant data meta-analysis largely align with those of previous meta-analyses.[14,27,28]

Our moderation analyses suggesting that preventive effects are more pronounced in the subgroups with initial moderate and moderately severe depressive symptoms partially validate previous research on preventive interventions for depression.[13] Of eight studies in a systematic review on symptom severity as a moderator, half supported this effect, whereas one found

lower symptom burden increased efficacy.[13] Our finding that higher initial anxiety symptoms (GAD ≥10) improve intervention outcomes aligns with previous research.[13] Unlike previous studies,[13,14] we did not find age to be a moderating factor. However, previous research focused on specific populations (eg, female caregivers) and delivery formats (eg, internet interventions).

Our findings support guidelines recommending psychological interventions as a treatment option in the management of subthreshold persistent depressive symptoms.[29] Moreover, our results underscore the importance of public health messaging that emphasises the effectiveness of preventive psychological interventions for depression, contributing to de-stigmatisation and encouraging widespread engagement in mental health practices. Future research should explore strategies for integrating preventive interventions into routine care settings, acknowledging the current gap in implementation of preventive interventions.[30]

Our findings suggest that the provision of subgroup-specific, tailored interventions based on factors such as sex, age, ethnicity, education, employment status, relationship status, presence of chronic medical conditions, history of MDD, and intake of anti-depressive medication might not be warranted. These insights might support a universal applicability of psychological interventions across diverse demographic and clinical groups. However, ethnicity is often used as a proxy for culture, although they are distinct. Culturally tailored interventions improve engagement, retention, and overall effectiveness.[31] Targeting individuals' specific challenges and tailoring content to their experiences is crucial for successful preventive interventions. Additional research is essential to evaluate the potential of preventive psychological interventions in subgroups with mild initial symptom severity. Specifically, investigations are needed to identify the point at which depressive and anxiety symptoms at the lower end of the severity spectrum become persistent enough to warrant preventive interventions. Although a history of MDD did not act as an effect modifier, it was assessed in only 11 (37%) of 30 studies, and we could not assess if a threshold of previous episodes affects intervention effectiveness. Further research is warranted to explore methods for enhancing preventive effects in individuals with previous exposure to psychotherapy. Our findings suggest that a preventive effect might not extend up to 24 months, although available data are scarce. This finding is consistent with the evidence observed in children and adolescents.[32] Future research is needed to explore how interventions might be revised or refined to stabilise their impact. Although conference calls showed stronger preventive effects, the low number of studies (two) prevents drawing definitive conclusions about their superiority. The possibility that various delivery formats and intervention types might have similar effects in preventing MDD might motivate a shared decision-making process and a personalised, patient-centred approach to intervention selection based on individual needs, preferences, and considerations of accessibility and convenience. However, more research is needed to determine whether these different formats and intervention types truly have similar effects.

	Number of studies	Incidence rate ratio (95% CI)	τ^2	p value
Region				
North America	7	0·76 (0·48–1·21)	0·000	0·252
Europe	17	0·68 (0·54–0·87)	0·000	..
Australia	3	0·68 (0·34–1·36)	0·000	..
Asia	4	0·34 (0·19–0·62)	0·000	..
Other	1	0·53 (0·17–1·61)	-	..
Intervention type				
Problem-solving therapy	4	0·62 (0·36–1·06)	0·158	0·374
Cognitive behaviour therapy	16	0·69 (0·54–0·89)	0·083	..
Behavioural activation	4	0·54 (0·27–1·08)	0·000	..
Stepped care	5	0·78 (0·45–1·37)	0·000	..
Other	3	0·32 (0·15–0·69)	0·207	..
Delivery type				
Face to face	12	0·71 (0·52–0·97)	0·000	0·002
Other	8	0·63 (0·41–0·96)	0·000	..
Conference call*	2	0·24 (0·11–0·53)	0·000	..
Internet	8	0·63 (0·43–0·92)	0·186	..
Publication year				
Until 2010	7	0·77 (0·54–1·11)	0·000	0·453
Until 2015	10	0·54 (0·35–0·84)	0·337	..
After 2015	15	0·63 (0·47–0·84)	0·090	..
Control group				
Care as usual	24	0·68 (0·54–0·84)	0·000	0·337
Other	8	0·52 (0·32–0·85)	0·372	..
Risk of bias				
Low	24	0·62 (0·50–0·77)	0·000	0·366
Some concerns	3	0·94 (0·52–1·69)	0·000	..
High	5	0·50 (0·21–1·19)	0·578	..

*Each of the two studies encompasses two distinct comparisons: Vázquez et al, 2017a and Vázquez et al, 2020a compared behavioural activation and control. Vázquez et al, 2017b and Vázquez et al, 2020b compared cognitive behavioural therapy and control.

Table 3: **Results of study-level moderator analyses**

Our systematic review and individual participant data meta-analysis has several limitations. First, we were not able to retrieve data from all eligible randomised controlled trials, with data obtained from 30 of 42 studies. Second, between-study heterogeneity was moderate to large in many analyses, indicating that true effects might differ across contexts. Third, not all studies provided data at all assessment points, which means that systematic differences among trials could cause different effects across time. Trials reporting outcomes at 24 months

often did not provide efficacy data for earlier timepoints. Fourth, we could not include certain putative moderators in our analyses due to insufficient data in the included studies, such as childhood adversity, quality of life, mastery (ie, locus of control), or racial, ethnic, and cultural diversity. Improved consistency in assessing relevant effect modifiers in depression prevention studies would enable more sophisticated treatment-covariate interaction analyses, for example by using core outcome sets.Establishing core outcome sets for psychological depression prevention could be a promising direction for future research. Last, the sample's demographic composition, with half of participants having higher education and 70% being female, might limit the generalisability of the findings. However, neither education nor sex were identified as effect modifiers.

We conclude that psychological interventions for depression prevention might serve as an effective strategy to alleviate the disease burden of depression at an individual and societal level. Our findings contribute to estimating the benefits of preventive interventions for clinicians and policy makers. Given the significant burden of depression, clinicians and policy makers should consider preventive psychological interventions as a viable option for individuals with subthreshold depression.

IPD-PrevDep Consortium
Marcel C Adriaanse (Department of Health Sciences and Amsterdam Public Health Research Institute, Vrije Universiteit Amsterdam, Amsterdam, Netherlands), Steven M Albert (Department of Behavioral and Community Health Sciences, Graduate School of Public Health, University of Pittsburgh, PA, USA), Esther Allart (Allart Supervisie, Nijmegen, Netherlands), Osvaldo P Almeida (Medical School, University of Western Australia, WA, Australia; Institute for Health Research, University of Notre Dame Australia, Fremantle, WA, Australia), Julian Basanovic (Department of Psychology, University of Exeter, Exeter, UK; School of Psychological Science, University of Western Australia, WA, Australia), Philip J Batterham (Centre for Mental Health Research, College of Health and Medicine, Australian National University, Canberra, ACT, Australia), Harald Baumeister (Department of Clinical Psychology and Psychotherapy, Ulm University, Ulm, Germany), Thomas Berger (Institute of Psychology, University of Bern, Bern, Switzerland), Vanessa Blanco (Department of Evolutionary and Educational Psychology, University of Santiago de Compostela, Santiago de Compostela, Spain), Robin Casten (Sidney Kimmel Medical College of Thomas Jefferson University, Philadelphia, PA, USA), Dicken Chan (School of Public Health and Primary Care, Chinese University of Hong Kong, Hong Kong, China), Helen Christensen (Black Dog Institute, Sydney, Australia; School of Psychiatry, Faculty of Medicine, University of New South Wales, Sydney, NSW, Australia), Marketa Ciharova (Department of Clinical Neuro- and Developmental Psychology, VU University Amsterdam, Amsterdam, Netherlands), Lorna Cook (SMART Lab, Mood Disorders Centre, Department of Psychology, University of Exeter, Exeter, UK), Keith S Dobson (Department of Psychology, University of Calgary, Calgary, AB, Canada), Elsien Dozeman (GGZ inGeest, Specialized Mental Health Care, Amsterdam, Netherlands), Kotaro Imamura (Department of Digital Mental Health, Graduate School of Medicine, University of Tokyo, Tokyo, Japan), Michael R Irwin (Cousins Center for Psychoneuroimmunology, Jane and Terry Semel Institute for Neuroscience and Human Behavior, David Geffen School of Medicine, University of California, Los Angeles, CA, USA; Department of Psychiatry and Biobehavioral Sciences, David Geffen School of Medicine, University of California, Los Angeles, CA, USA), Norito Kawakami (Department of Digital Mental Health, Graduate School of Medicine, University of Tokyo, Tokyo, Japan), Eirini Karyotaki (Department of Clinical Neuro- and Developmental Psychology, VU University Amsterdam, Amsterdam, Netherlands), Jan Philipp Klein (Department of Psychiatry, Psychosomatics, and Psychotherapy, University of Lübeck, Lübeck, Germany; Center for Brain, Behavior, and Metabolism, University of Lübeck, Lübeck, Germany), Candace Konnert (Department of Psychology, University of Calgary, Calgary, AB, Canada), María Asunción Lara (Dirección de Investigaciones Epidemiológicas y Psicosociales, Instituto Nacional de Psiquiatría Ramón de la Fuente Muñiz, Ciudad de México, México), Huynh-Nhu Le (Department of Psychological and Brain Sciences, George Washington University, Washington, DC, USA), Dirk Lehr (Department of Health Psychology and Applied Biological Psychology, Institute of Psychology, Leuphana University Lueneburg, Lueneburg, Germany), Steffen Moritz (Department of Psychiatry and Psychotherapy, University Medical Center Hamburg-Eppendorf, Hamburg, Germany), Ricardo F Muñoz (Department of Psychology, Palo Alto University, Palo Alto, CA, USA; Department of Psychiatry and Behavioral Sciences, University of California, San Francisco, CA, USA), Richard Olmstead (Cousins Center for Psychoneuroimmunology, Jane and Terry Semel Institute for Neuroscience and Human Behavior, David Geffen School of Medicine, University of California, Los Angeles, CA, USA; Department of Psychiatry and Biobehavioral Sciences, David Geffen School of Medicine, University of California, Los Angeles, CA, USA), Patricia Otero (Department of Psychology, University of A Coruña, A Coruña, Spain), Charles F Reynolds III (Department of Psychiatry, University of Pittsburgh School of Medicine, Pittsburgh, PA, USA), Barry W Rovner (Sidney Kimmel Medical College of Thomas Jefferson University, Philadelphia, PA, USA), Lasse B Sander (Medical Psychology and Medical Sociology, Faculty of Medicine, University of Freiburg, Freiburg, Germany), Filip Smit (Department of Mental Health and Prevention, Trimbos Institute, Utrecht, Netherlands; Department of Epidemiology and Biostatistics, Amsterdam University Medical Centers, Amsterdam, Netherlands), Philip Spinhoven (Department of Clinical Psychology, Institute of Psychology, Leiden University, Netherlands), Liza Stelmach (Carewest, Calgary, AB, Canada), Yannik Terhorst (Department of Psychology, Ludwig Maximilian University of Munich, Munich, Germany and German Center for Mental Health (DZPG), Partner-Site Munich-Augsburg, Munich, Germany), Fernando L Vázquez (Department of Clinical Psychology and Psychobiology, University of Santiago de Compostela, Santiago de Compostela, Spain), Ed Watkins (SMART Lab, Mood Disorders Centre, Department of Psychology, University of Exeter, Exeter, UK), Godelief R W M Willemse (Vilans, Utrecht, Netherlands), Wenhui Yang (Department of Psychology, Hunan Normal University, Changsha, Hunan, China), Samuel Y S Wong (School of Public Health and Primary Care, Chinese University of Hong Kong, Hong Kong, China).

For the **Metapsy website** see https://docs.metapsy.org/databases/depression-psyctr/

Contributors
CB, DDE, and PC conceived and designed the study. CB, MH, AAS, and SI selected the studies and extracted data. CB, DDE, PC, and members of the IPD-PrevDep Consortium contributed the individual participant data. MH, AAS, and SI verified the data. MH analysed the data. CB, MH, MS, TAF, and PC interpreted the results. CB and MH wrote the first draft of the manuscript. All authors had access to all the data and provided critical input and revisions to the draft manuscripts and approved the final manuscript. CB and PC had final responsibility for the decision to submit for publication.

Data sharing
All extracted data are available in the manuscript and appendix, as well as on the Metapsy website. Individual-level data cannot be made available due to confidentiality agreements in the original studies.

Declaration of interests
DDE is a stakeholder of the Institute for health training online (GET.ON), which aims to implement scientific findings related to digital health interventions into routine care. MS is employed through a grant provided by the Nagoya City. TAF reports personal fees from Boehringer-Ingelheim, Daiichi Sankyo, DT Axis, Kyoto University Original, Shionogi, SONY, and UpToDate, and a grant from DT Axis and Shionogi, outside of the submitted work; TAF has a patent (7448125), a pending patent (2022–082495), and intellectual properties for Kokoro-app licensed to Mitsubishi-Tanabe. All other authors declare no competing interests.

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