

Review



Psychological interventions to prevent the onset of depressive disorders: A meta-analysis of randomized controlled trials

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ABSTRACT

Purpose: Depressive disorders are common and have a considerable impact on patients and societies. Several treatments are available, but their effects are modest and reduce the burden only to a limited extent. Preventing the onset of depressive disorders may be one option to further reduce the global disease burden.

Methods: We conducted a meta-analysis of randomized controlled trials in participants without a diagnosis of depression at baseline, who were assigned to a preventive psychological intervention, or a care-as-usual, or comparable control group and in which incident cases of depression at follow-up were ascertained with a diagnostic interview.

Results: Our systematic searches resulted in 50 trials (14,665 participants) with relatively high quality, in high risk groups of all ages. The psychological interventions were mostly based on cognitive behavioral interventions. One year after the preventive interventions, the relative risk of developing a depressive disorder was $RR = 0.81$ (95% CI: 0.72–0.91), indicating that those who had received the intervention had 19% less chance to develop a depressive disorder. Given the average control event rate of 30%, twenty-one people had to participate in the intervention to prevent one depressive disorder compared to people in the control conditions.

Conclusions: Prevention is a promising approach to reduce the global disease burden of depression in addition to treatments.

1. Introduction

Depressive disorders are very common with more than 300 million people, or 4.4% of the world population affected (World Health Organisation, 2017). Depression is also the single largest contributor to global disability and is responsible for 7.5% of all years with disability worldwide (GBD 2016 Disease and Injury Incidence and Prevalence Collaborators, 2017; World Health Organisation, 2017). Depression is also associated with considerable morbidity and mortality (Cuijpers et al., 2014), and high economic costs (Bloom et al., 2011; Hu, 2006). Several treatments are available for depression, with pharmacotherapy

and psychotherapy as first line treatments. Although these treatments are effective, the effects of both pharmacotherapy and psychotherapy are modest (Barth et al., 2013; Cipriani et al., 2018), relapse rates are high and a considerable group of patients do not respond to treatments at all (Cuijpers, Karyotaki, & Ciharova, 2020; Cuijpers et al., 2020; Cuijpers, Stringaris, & Wolpert, 2020). A modelling study has shown that available treatments can reduce the disease burden of depression on a population level by only one third (Andrews, Issikadis, Sanderson, Corry, & Lapsley, 2004), and this is only under optimal conditions, assuming that all people with depression are treated with an evidence-based treatment. In reality, the number of people receiving treatment

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is less than 50%, even in high-income countries (Chisholm et al., 2016).

Preventing the onset of depressive disorders could be an alternative method to reduce the disease burden of depression and prevent personal suffering of patients (Cuijpers, Beekman, & Reynolds, 2012; Muñoz, 2019). Starting in the late 1980s, a growing number of randomized trials have examined the possibilities to prevent the onset of depressive disorders. Several hundreds of studies have examined the effects of preventive interventions for depression in many different target groups and settings (Cuijpers, van Straten, Smit, Mihalopoulos, & Beekman, 2008). However, only a limited number of studies have examined the effects of preventive interventions on the incidence of new diagnosed depressive disorders in those with no depressive disorder at baseline. In the past 25 years, the number of such trials, in which all participants had a diagnostic psychiatric interview to exclude those meeting criteria for a depressive disorder at baseline, and another interview to examine the incidence of depressive disorders at follow-up, has increased considerably.

There are three types of prevention (Institute of Medicine, 2009). Universal prevention is aimed at a whole population, regardless of the risk of developing depressive disorders, including for example school programs aimed at developing life skills or mass media campaigns. Selective prevention is aimed at high-risk groups, such as children of depressed parents, unemployed people, or people who experienced trauma recently or in the past. Indicated prevention is aimed at people who already have some symptoms, but do not meet criteria for a full-blown depressive disorder, this state is often called subthreshold or minor depression. These three types of interventions have in common that they are aimed at people who do not currently have a depressive disorder. Interventions aimed at people who meet criteria for a disorder are all in the domain of treatment or maintenance treatment.

We have previously conducted several earlier meta-analyses of randomized trials aimed at all three types of prevention of depressive disorders (Cuijpers et al., 2008; Van Zoonen et al., 2014), which showed that preventive interventions can reduce the incidence of depression about 20% compared to no intervention. However, since the last update of this meta-analysis (Van Zoonen et al., 2014) a considerable number of new trials have been conducted. Including a higher number of studies makes it possible to examine the effects of preventive interventions more precisely, to examine the impact of bias in these studies and publication bias more extensively, and to better examine the effects in specific subgroups. Several other meta-analyses in the prevention field have been conducted, but these have typically not focused on studies excluding participants with a diagnosis at baseline (Hetrick, Cox, Witt, Bir, & Merry, 2016; Muñoz, Cuijpers, Smit, Barrera, & Leykin, 2010), or have only examined specific subgroups or settings (e.g., Bellón et al., 2019; Thanhäuser, Lemmer, de Girolamo, & Christiansen, 2017).

We decided therefore, to conduct a new, comprehensive meta-analysis of randomized trials comparing the effects of psychological interventions with care-as-usual or comparable control groups in people who do not meet criteria for a depressive disorder, and in which these interventions were aimed at preventing the onset of depressive disorders at follow-up.

2. Methods

2.1. Identification and selection of studies

The protocol for this meta-analysis was registered at the Open Science Framework (Cuijpers, Karyotaki, & Ciharova, 2020; Cuijpers, Karyotaki, Quero, et al., 2020; Cuijpers, Stringaris, & Wolpert, 2020). To identify studies, we used an existing database of randomized trials on the psychological treatment of depression. This database has been described in detail elsewhere (Cuijpers, Karyotaki, & Ciharova, 2020, Cuijpers, Karyotaki, Quero, et al., 2020, Cuijpers, Stringaris, & Wolpert, 2020), and has been used in a series of earlier published meta-analyses (Cuijpers, 2017). The protocol for the current meta-analysis has been

registered at the Open Science Foundation as part of the main meta-analytic project (<https://osf.io/p8r52>).

For the meta-analytic database, we searched four major bibliographical databases (PubMed, PsycINFO, Embase, and the Cochrane Library) by combining terms (both index terms and text words) indicative of depression and psychotherapies, with filters for randomized controlled trials. We also searched a number of bibliographical databases to identify trials in non-Western countries (Cuijpers, Karyotaki, Reijnders, Purgato, & Barbui, 2018), because the number of trials on psychological treatments in these countries is growing rapidly. Furthermore, we checked the references of earlier meta-analyses on psychological treatments of depression. The database is continuously updated and was developed through a comprehensive literature search (from 1966 to 1 January 2020).

Because in this database only trials on indicated prevention are included (aimed at participants who have some symptoms of depression, but do not need full diagnostic criteria for a depressive disorder), additional searches were conducted in PubMed, PsycINFO and the Cochrane database. These searches were aimed to identify randomized trials on universal (aimed at whole populations) and selective prevention (aimed at high risk groups). In these searches we combined key words and text words for depression, prevention and randomized trials. The full search strings for the main database and the additional searches are given in Appendix A (PubMed). Deadline for the searches was November 14, 2019. In addition, we also checked the references of previous meta-analyses of trials on prevention of depressive disorders (Bellón et al., 2019; Cuijpers et al., 2008; Hetrick et al., 2016; Loechner et al., 2018; Muñoz et al., 2010; Thanhäuser et al., 2017; Van Zoonen et al., 2014).

All records were screened by two independent researchers. All papers that could possibly meet inclusion criteria according to one of the researchers were retrieved as full-text. The decision to include or exclude a study in the database was also done by the two independent researchers, and disagreements were solved through discussion.

We included studies meeting the following criteria: (1) participants did not meet criteria for current clinical episode of a depressive disorder at baseline, as established with a diagnostic interview by a trained interviewer or clinician; (2) participants were randomly assigned to a psychological preventive intervention or a control group; (3) the incidence in the intervention and control conditions at follow-up (at least 3 months after randomization) was measured through a diagnostic interview by a trained interviewer or clinician; (4) sufficient data were reported to calculate the incidence rates in the intervention and control conditions. Any control group was acceptable, as long as it was defined by the researchers as a control group. Studies aimed at relapse prevention, in which all participants were (partly) recovered from depression through treatment, were excluded.

2.2. Quality assessment and data extraction

We assessed the validity of included studies using four criteria of the 'Risk of bias' assessment tool, developed by the Cochrane Collaboration (Higgins et al., 2011). The risk of bias tool assesses possible sources of bias in randomized trials, including the adequate generation of allocation sequence; the concealment of allocation to conditions; the prevention of knowledge of the allocated intervention (masking of assessors); and dealing with incomplete outcome data. Assessment of risk of bias was conducted by two independent researchers, and disagreements were solved through discussion.

We also coded other characteristics of the studies: type of prevention (indicated, selective, universal), target group, time to follow-up (in months), proportion of participants with a history of depression, type of intervention (cognitive behavior therapy (CBT), interpersonal psychotherapy (IPT), other), format of the intervention (individual, group, other), number of sessions, country where the study was conducted.

2.3. Outcome measures

Primary outcome was the Relative Risk (RR) of developing a depressive disorder at 12 months follow-up or the closest time point to 12 months follow-up (incidence). Incidence was calculated using an 'intention-to-treat approach'. This means that in studies in which missing data at follow-up have been imputed, these imputed data were used for the calculation of incidence. In studies that have not imputed missing data, we considered those who dropped out of the study since randomization as new incident cases.

Secondary outcomes include the RR of developing a depressive disorder using completers only data (in which subjects that have dropped out of the study are excluded), and acceptability of the interventions (defined as study drop-out for any reason). We also calculated the number needed to be treated (NNT; Laupacis, Sackett, & Roberts, 1988), indicating the number of participants that have to receive the intervention in order to prevent one depressive disorder compared to no intervention. The NNT was calculated using the the pooled RR and the expected control event rate (the weighted pooled event rate of all the control conditions).

2.4. Meta-analyses

To calculate pooled RRs, we used the "metafor" package in R and ran all analyses in R studio (version 1.1.463 for Mac). Because we expected considerable heterogeneity among the studies, we employed a random effects model in all analyses. We pooled RRs using the inverse variance method, with the Hartung-Knapp adjustment for the random effects model. For the assessment of heterogeneity, we calculated I^2 and its 95% confidence interval (CI), an indicator of heterogeneity in percentages (Higgins, Thompson, Deeks, & Altman, 2003). A value of 0% indicates no observed heterogeneity, and larger values indicate increasing heterogeneity, with 25% as low, 50% as moderate, and 75% as high heterogeneity (Higgins et al., 2003).

We tested for publication bias by inspecting the funnel plot and by Duval and Tweedie's trim and fill procedure (Duval & Tweedie, 2000), which yields an estimate of the RR after taking publication bias into account. We also conducted Peters' method to test whether the funnel plot is asymmetrical (Peters, Sutton, Jones, Abrams & Rushton, 2006). In addition, we calculated the prediction interval, which indicates the range in which the true effect size of 95% of future studies will fall (Borenstein, Higgins, Hedges, & Rothstein, 2017).

To examine differences between subgroups of studies, we conducted subgroup analyses according to the mixed effects model. In this model effect sizes within subgroups are pooled according to the random effects model and the difference between subgroups according to a fixed effects model. For continuous variables, we used bivariate meta-regression analyses to test whether there was a significant relationship between the continuous variable and effect size. Multivariate meta-regression analyses were conducted, with the effect size as the dependent variable and the predictors from subgroup analyses (as dummy variables) and continuous variables.

Several sensitivity analyses were conducted. First, we included only studies with low risk of bias. Second, we excluded studies whose main follow-up assessment was outside the range of 6 to 18 months follow-up. We did this because the time between randomization and the assessment of incidence varied considerably across studies. Third, because only one study on universal prevention was included, we also conducted a sensitivity analysis in which this study was excluded. Fourth, in some studies, more than one psychological intervention was compared with the control group. In the main analyses we pooled the outcomes for these interventions so that each study had only one effect size. We conducted sensitivity analyses in which these studies were excluded.

3. Results

3.1. Selection and inclusion of studies

After examining a total of 5210 abstracts (4085 after removal of duplicates), we retrieved 480 full-text papers for further consideration. We excluded 430 of the retrieved papers. The PRISMA flowchart describing the inclusion process, including the reasons for exclusion, is presented in Fig. 1. A total of 50 randomized controlled trials, with 12,006 participants (6133 in the preventive interventions; 5873 in the control conditions) met inclusion criteria for this meta-analysis. References of the trials are given in Appendix B.

3.2. Characteristics of included studies

A summary of key characteristics of the included studies are presented in Table 1. A total of 33 studies examined an indicated preventive intervention (66%), 16 were focused on a selective preventive intervention (32%) and one study was focused on universal prevention (2%). Twenty-five studies were aimed at adults (50%), 14 on children and adolescents (28%) and 11 on older adults (22%). Nine studies were aimed at prevention of perinatal depression (18%), 11 were aimed at patients with general medical conditions (22%) and 5 were aimed at college students (10%). Twenty studies reported the proportion of participants who previously had a depressive disorder. In these studies, the proportion of participants who previously had a depressive disorder ranged from 0.6% to 67% with a median of 34.5%. The mean age of participants ranged from 11.4 to 84.4 years of age (median 29.2 years).

Most interventions (22; 44%) were based on CBT, 8 on IPT (16%), 5 used a stepped care model (10%), 5 used problem-solving (10%), and 10 used other types of intervention (20%), such as behavioral activation, acceptance and commitment therapy, cognitive bias modification. The intervention format was individual in 16 studies (32%), group in 19 studies (38%) and the other 15 studies used another or a mixed format (30%). The number of sessions ranged from 4 to 44 (median 8), but most interventions had between 5 and 16 sessions (39 of the 44 studies that reported the number of sessions; 88.6%).

Most studies used a care-as-usual control condition (37; 74%). A total of 26 studies were conducted in the US (52%), 17 in Europe (34%) and 7 in other countries (14%), including Australia (3 studies), China (2 studies), Canada (1 study) and India (1 study). The risk of bias was relatively low in this sample of studies. A total of 41 studies reported an adequate sequence generation (82%), 26 studies reported allocation to conditions by an independent (third) party (52%), 38 studies reported using blinded outcome assessors (76%), and in 40 studies intent-to-treat analyses were conducted (80%). A total of 22 studies (44%) met all quality criteria, 16 met 2 or 3 criteria (32%), and the remaining 12 studies met no or only one criterion (24%). Risk of bias of individual studies is reported in Table 1 and the overall risk for all studies together is reported in Appendix C.

3.3. Effects of preventive interventions on incidence of depressive disorders

The pooled RR of developing a depressive disorder at 1-year follow-up in the preventive interventions was RR = 0.81 (95% CI: 0.72–0.91) compared to the control conditions, indicating that the risk of developing depression was reduced by 19%. The forest plot with the RRs for each study are presented in Fig. 2 and the main outcomes are given in Table 2. Heterogeneity was low to moderate ($I^2 = 36%$; 95% CI: 9–55). The prediction interval ranged from 0.25 to 1.88.

There was some risk for publication bias. Duval and Tweedie's trim and fill procedure indicated 8 missed studies. The adjusted effect size was still significant, however (RR = 0.86; 95% CI: 0.75–0.99). Peters' test of the asymmetry of the funnel plot also pointed as a risk for publication bias ($p = 0.002$). The NNT was 18.8.

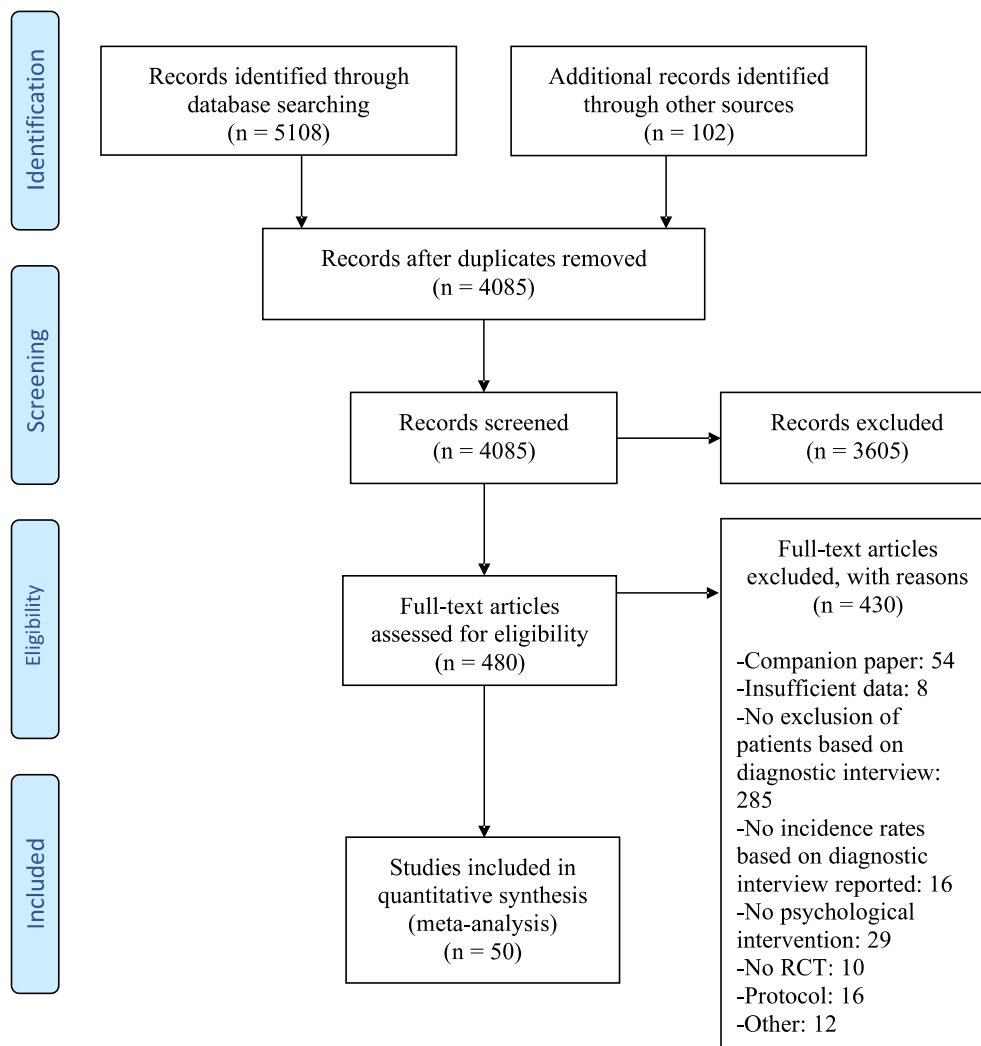


Fig. 1. Flowchart of the selection of studies.

The results of the sensitivity analyses are reported in Table 2. The analyses in which only included outcomes measured between 9- and 15-months follow-up resulted in outcomes that were very comparable to the main analyses. The same was true when the study on universal prevention was excluded and when the studies with multiple intervention arms were excluded. In the studies with low risk of bias, the RR was a little larger (closer to 1) than the RR found in the main analyses, but the RR was no longer significant. This may be related to lower statistical power. When outcomes were measured in completers only, the RR was, as could be expected, somewhat stronger (RR = 0.64; 95% CI: 0.56–0.75). Heterogeneity was low to moderate in all analyses.

We also examined acceptability and the effects of the interventions on incidence of depression at the longer term. Acceptability was somewhat better in the control conditions than in the interventions (RR = 1.21; 95% CI: 1.00–1.45) although that was not significant. Heterogeneity was moderate in these analyses ($I^2 = 48$; 95% CI: 26–64). At the longer term (2–3 years, and 3–8 years) the effects in incidence were no

longer significant, although the number of studies was small and may not have enough statistical power to find significant effects.

3.4. Subgroup and meta-regression analyses

We conducted a series of subgroup analyses. The results of these analyses are reported in Table 3. In the analyses in which type of prevention was examined, we found that both indicated and selective prevention had significant effects. Only one study examined the effects of universal prevention. The difference between the effects found for the three types of prevention were not significant.

We examined several other subgroups (age groups; specific target groups; intervention type; format, care-as-usual versus other control groups; country; and risk of bias). None of these subgroup analyses indicated significant differences between the effects found in subgroups. The only significant difference was for country, where the effects for the US were the strongest, also significant effects for Europe, but a much

Table 1
Selected characteristics of included studies.

Study	Prev type	Target group	Age group	Prop. history	Mean age	Prop. women	Intervention	Format	N sess	country	ctr	RoB	SG	AC	BA	ITT
Albert, 2019	I	older adults with home care needs	Older				pst	Ind	7	US	cau	mod	+	±	+	+
Allart, 2007	I	Subthreshold depression	Adult	59.1	45.5	0.62	cbt	Group	12	NL	cau	high	+	±	±	±
Arnarson, 2009	I	Subthreshold depression	Adol		14.5	0.51	cbt	Group	14	ICE	cau	high	±	±	+	-
Basanovic, 2019	I	Subthreshold depression	Adult	59.4	60.2	0.49	cbm	other	44	AUS	other	low	+	+	+	+
Bellon, 2016	S	Subthreshold depression & high risk primary care patients	Adult	34.5	50.7	0.64	sup	Ind		SP	cau	mod	±	+	+	+
Bot, 2019	I	adults with overweight	Adult	33.5	45.9	0.73	bat	mixed	21	EU	other	low	+	+	+	+
Buntrock, 2016	I	Subthreshold depression	Adult		45.04	0.74	pst + bat	3	6	GER	cau	low	+	+	+	+
Clarke, 2001	I	children of depressed parents	Adol	67	14.55	0.64	cbt	Group	15	US	cau	low	+	+	+	+
Clarke, 1995	I	Subthreshold depression	Adol	38	15.3	0.70	cbt	Group	15	US	cau	high	±	±	±	±
Compas, 2009	S	children depressed parents	Adol		11.4	0.45	cbt	Group	12	US	other	low	+	+	+	+
Cook, 2019	S	high on worrying	Adult	39.1	20.41	0.83	cbt/cbm	3	6	UK	cau	low	+	+	+	+
De Jonge, 2009	S	medically ill	Adult		52.93	0.58	coll care	Ind	8	SWI	cau	mod	+	±	+	+
Dias, 2019	I	older adults	Older		69.6	0.63	cbt + pst	Ind	6	INDIA	cau	low	+	+	+	+
Dozeman, 2012	I	older adults in residential homes	Older	54.9	84.4	0.73	stepped care	Ind		NL	cau	low	+	+	+	+
Garber, 2009	I	children of depressed parents	Adol	55.4	14.8	0.59	cbt	Group	14	US	cau	mod	+	±	-	+
Garcia, 2010	S	patients with somatoform disorders	Adol		32.3	0.73	cbt	Group	5	SP	cau	low	+	+	+	+
Hagan, 2004	S	Perinatal caregivers	Adult	36.2	29.2	1.00	cbt	Group	6	AUS	cau	low	+	+	+	+
Joling, 2012	S	dementia patients	Older		69.5	0.70	other	mixed	5	NL	cau	low	+	+	+	+
Karp, 2019	I	Knee Osteoarthritis	Older	33.3	71	0.62	cbt	Ind	8	US	cau	mod	+	±	+	+
Konnert, 2009	I	nursing home residents	Older		81.1	0.77	cbt	Group	13	CAN	cau	high	+	±	-	-
Martinovic, 2006	I	adolescents with epilepsy	Adol		17.4	0.60	cbt	Ind	8	SERV	cau	high	+	-	-	±
Muñoz, 1995	S	primary care patients	Adult		52.4	0.62	cbt	Group	8	US	cau	high	±	±	±	±
Muñoz, 2007	I	Perinatal	Adult	53.7	24.9	1.00	cbt	Group	16	US	cau	high	±	+	±	-
Otero, 2015	I	caregivers	Adult		53.9	73.4	pst	Group	5	SP	cau	low	+	+	+	+
Phipps, 2013	S	Perinatal	Adol	16	16	1.00	ipt	mixed	5	US	other	low	+	+	+	+
Pols, 2017	I	diabetes 2 and heart disease patients	Adult		67.5	0.45	stepped care	Ind		NL	cau	low	+	+	+	+
Robinson, 2008	I	stroke patients	Older	5.1	65.6	0.43	pst	Ind	12	US	other	low	+	+	+	+
Rohde, 2014	I	high school students	Adol		15.5	0.68	cbt	mixed		US	other	mod	+	-	+	+
Rohde, 2014B	I	college students	Adult		19	0.70	cbt	mixed		US	other	mod	+	-	+	+
Rohde, 2016	I	college students	Adult		21.8	0.68	cbt	Group	6	US	other	mod	+	-	+	+
Rovner, 2007	S	Age-Related Macular Degeneration	Older		81.2	0.70	pst	Ind	6	US	cau	low	+	+	+	+
Rovner, 2014	I	Age-Related Macular Degeneration	Older		84	0.70	bat	Ind	6	US	other	low	+	+	+	+
Seligman, 1999	S	college students at risk because of attributable style	Adult			0.52	cbt	Group	8	US	cau	high	±	±	+	-
Silverstein, 2017	I	Head Start mothers	Adult	42.2	31.3	1.00	pst	Ind	6	US	cau	low	+	+	+	+
Spence, 2003	U	students high school	Adol		12.85	0.53	pst + cr	Group	8	AUS	cau	high	±	±	-	+
	I		Adol		15.6	0.56	mixed	Group	6	US	cau	mod	+	-	+	+

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Table 1 (continued)

Study	Prev type	Target group	Age group	Prop. history	Mean age	Prop. women	Intervention	Format	N sess	country	ctr	RoB	SG	AC	BA	ITT
Stice, 2008 - cbt		high school students														
Tandon, 2018	S	Perinatal	Adult		26.13	1.00	cbt	Ind	12	US	cau	mod	+	±	±	+
Van 't Veer, 2009	I	older primary care patients	Older		81.4	0.74	stepped care	Ind		NL	cau	low	+	+	+	+
VanderAA 2015	I	visually impaired older adults	Older	20.8	73.7	0.70	stepped care	Ind		NL	cau	low	+	+	+	+
Vazquez, 2012	I	college students	Adult		23.3	0.82	cbt	Group	8	SP	other	high	±	+	+	±
Willemse, 2004	I	primary care patients	Adult		40.6	0.66	cbt	3	7	NL	cau	mod	+	±	+	+
Wong, 2018	I	primary care patients	Adult		54	0.93	act+mind	Group	8	CHINA	cau	low	+	+	+	+
Young, 2006	I	high school students	Adol	4.9	13.5	0.85	ipt	mixed	10	US	other	mod	+	±	+	+
Young, 2010	I	high school students	Adol	7	14.5	0.60	ipt	mixed	10	US	other	mod	+	±	+	+
Young, 2016	I	high school students	Adol		14.01	0.67	ipt	mixed	10	US	other	mod	+	±	+	+
Zhang, 2014	I	primary care patients	Adult		49	0.74	stepped care	Ind		CHINA	cau	low	+	+	+	+
Zlotnick, 2001	S	Perinatal	Adult	0.6	23.4	1.00	ipt	Group	4	US	cau	high	±	±	±	+
Zlotnick, 2006	S	Perinatal	Adult	31.3	22.4	1.00	ipt	mixed	5	US	cau	high	+	±	±	-
Zlotnick, 2011	S	low-income pregnant women with intimate partner violence	Adult		23.8	1.00	ipt	mixed	5	US	cau	mod	+	+	±	+
Zlotnick, 2016	S	mothers on public assistance	Adult		23	1.00	ipt	mixed	5	US	cau	mod	+	±	+	+

Abbreviations: Prev Type: type of preventive intervention; I: indicated; S: selective; U: Universal; Prop history: Proportion of participants with a history of depressive disorder; Prop. Women: Proportion of women; pts.: problem solving therapy; cbt: cognitive-behavioral therapy; cbm: cognitive bias modification; sup: supportive intervention; bat: behavioral activation therapy; ipt: interpersonal therapy; act+mind: acceptance and commitment + mindfulness intervention; Ind: Individual format; nsess: number of sessions; NL: the Netherlands; ICE: Iceland; AUS: Australia; SP: Spain; EU: Europe; GER: Germany; US: the United States; UK: United Kingdom; SWI: Switzerland; CAN: Canada; SERV: Serbia; ctr: control group; cau: care-as-usual; RoB: risk of bias; mod: moderate; SG: Sequence generation; AC: Allocation concealment; BA: Blinded assessment; ITT: Intention-to-treat analyses.

larger RR for other countries ($p < 0.001$).

We also conducted a multivariate meta-regression analysis (Table 4). None of the predictors was found to be significantly associated with the RR. In order to avoid overfit of the meta-regression model, we repeated this meta-regression analysis, with a (manual) stepwise backward elimination of the least significant predictor until only significant predictors remained in the model. This analysis resulted in only one significant predictor, namely whether the study was conducted in another country than the US or Europe (coefficient: 0.33, SE: 0.15, $p = 0.03$). The RR of studies in these countries was closer to 1.

4. Discussion

We identified a considerable number of trials ($n = 50$) examining the effects of psychological intervention on the incidence of new cases of depressive disorders at follow-up in people who did not have a depression at baseline. We found that these interventions can reduce the incidence at follow-up by 19%, with an NNT of 15. This remained significant in sensitivity analyses and at longer follow-up.

These findings confirm previous studies showing that it is actually possible to prevent the onset of depressive disorders in people who did not have such a disorder at baseline (Cuijpers et al., 2008; Van Zoonen et al., 2014). This is not true for all participants, but a considerable proportion of new disorders can be prevented, which is certainly important from a clinical perspective.

Previous meta-analyses only found significant effects for indicated prevention (Cuijpers et al., 2008; Van Zoonen et al., 2014), but in the current meta-analysis we also found significant effects for the group of selective interventions. Indicated prevention, in those with subthreshold

depression, can also be seen as early intervention in the prodromal phase of those who are already starting to develop the disorder. One could say, therefore, that it does not actually prevent the onset of depression, but only treats it in the early stages. However, as suggested by the “kindling hypothesis” preventing crossing the threshold into a full-blown clinical episode of depression may reduce “sensitization” to future stressful life events (Monroe & Harkness, 2005). Selective interventions in high risk groups, however, are applied in people who do not necessarily already have symptoms, and this certainly comes closer to “real” prevention. It is possible, however, that participants in selective interventions also have subthreshold depression and that it is this group that is responsible for the positive effects of the interventions on incidence.

We found no significant predictors of the effects, only the group of studies conducted outside the US and Europe had smaller effects. That may reflect a true difference between Western and non-Western countries, although that is exactly the opposite of what is found for psychological treatments of depression, which have been found to be more effective in non-Western countries (Cuijpers et al., 2018). However, this may also very well be an artefact, because of the small number of studies in this group, the low statistical power and the relatively large number of variables included in the meta-regression analyses. Only three of the 50 studies in our meta-analysis were conducted in middle income countries, two in China (Wong et al., 2018; Zhang et al., 2014) and one in India (Dias et al., 2019), and none in low-income countries. Because the majority of the world population lives in low and middle-income countries it is important that future studies examine the possibilities of preventive interventions in these settings.

In order to move the field forward, it is very important to identify significant moderators of outcome. Conventional meta-analyses are not

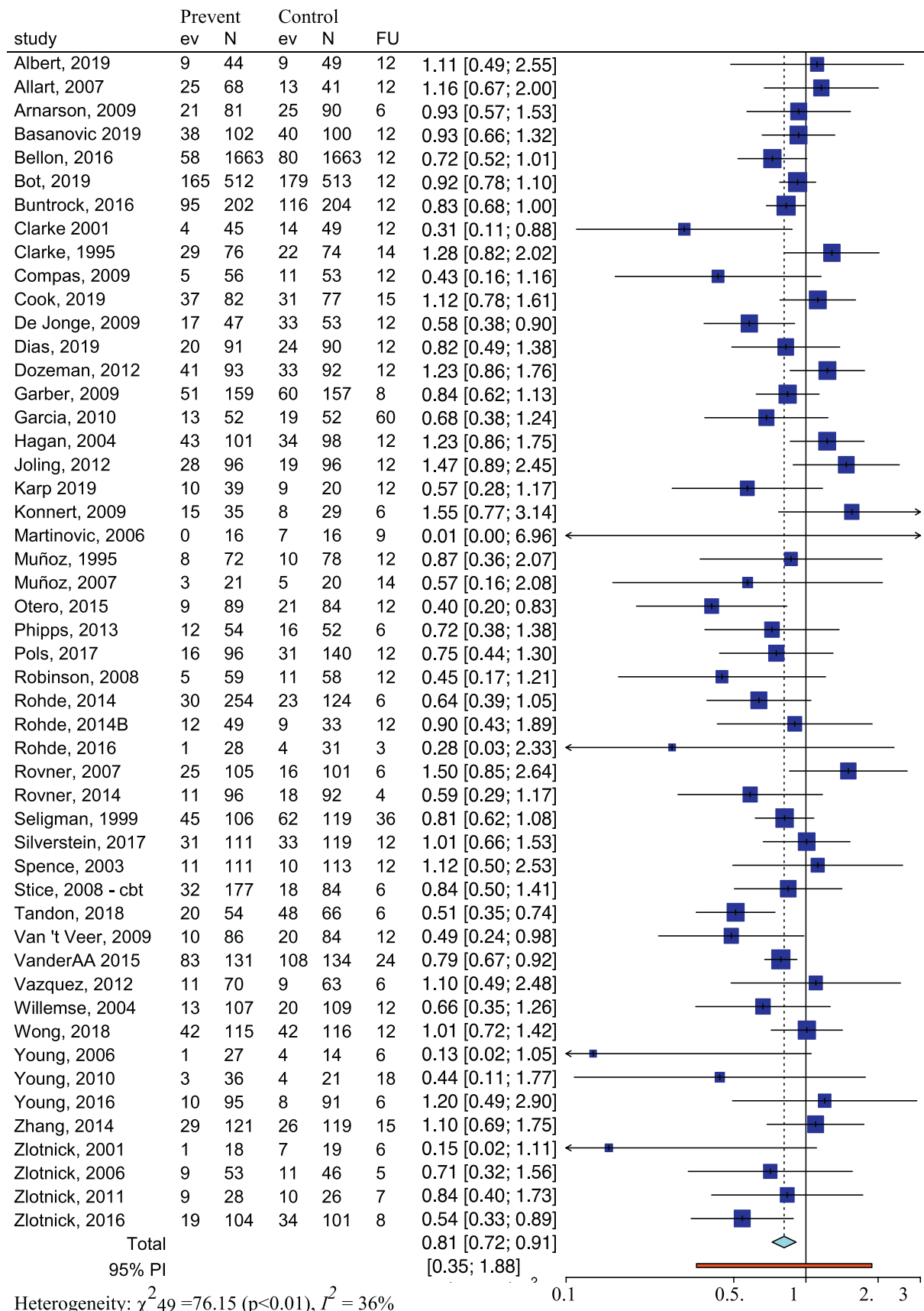


Fig. 2. Forest plot of preventive interventions versus control.

Table 2
Results of meta-analysis of randomized trials examining interventions aimed at preventing the onset of depressive disorders: Relative Risks^a.

	N _{comp}	RR	95% CI	I ²	95% CI
Main outcomes					
All studies at FU	50	0.81	0.72–0.91	36	9–55
Sensitivity analyses					
Adjusted for publication bias	58	0.86	0.75–0.99	41	19–57
Only low Risk of Bias	22	0.86	0.73–1.02	45	9–67
Limited to 9–15 months follow-up	29	0.85	0.73–0.98	36	0–59
Universal prevention excluded	49	0.81	0.72–0.91	37	10–55
Multiple arms excluded	47	0.81	0.72–0.92	39	12–57
Completers only	50	0.64	0.56–0.75	28	0–49
Other outcomes					
Acceptability	40	1.21	1.00–1.45	48	26–64
Outcome at 2 to 3 years	11	0.85	0.66–1.09	32	0–67
Outcome at 3 to 8 years	4	0.91	0.74–1.13	0	0–66

^a According to the random effects model.

well-suited to examine such moderators, because only moderators at the study level are available. However, ‘individual participant data’ (IPD) meta-analyses combine the primary data of randomized trials and have enough statistical power to identify such moderators. One recent IPD meta-analysis of indicated prevention of depression found for example that the effects of these interventions are stronger when baseline severity is higher (Reins et al., 2020). It is also important to consider biological risk markers in the further development of the field, although until now few markers have a sufficiently strong association to be clinically relevant (Penninx, Milaneschi, Lamers, & Vogelzangs, 2013).

It is encouraging that psychological interventions do seem to be effective in reducing the incidence of depression. Several studies examining other interventions have found negative effects, including interventions aimed at multinutrient supplements in obese people with subthreshold depression (Bot et al., 2019) and vitamin D3 (Okereke et al., 2020). These “negative” findings are also highly significant in that they illustrate the importance and superiority of large-scale experimental studies over observational studies in depression prevention.

One matter of concern was that we found that the studies with low risk of bias had a comparable effect size, but this was no longer significant, which may be because of a lack in statistical power. This means

that the findings still have to be considered with caution and it cannot definitely be concluded that preventive interventions are effective. More high-quality research is needed to confirm this.

One issue of concern is that, despite the apparent effects, few preventive interventions have been integrated into health care systems and implementation has been slow. Future research should focus not only on efficacy of interventions, but also on how to implement them in routine care settings, as this is clearly lagging behind (National Academies of Sciences, Engineering, and Medicine, 2019).

One of the strengths of this study is the relatively large number of included trials, their quality and the large number of participants, as well as the use of state-of-the-art methods to integrate the results of these studies. One important limitation is that participants, interventions and studies are very heterogeneous, and one could doubt whether integrating the results of these studies is indeed possible. However, all studies share basic characteristics, including inclusion criteria, outcome measures and the focus of the interventions on preventing the onset of depression. Furthermore, heterogeneity was small to moderate, suggesting that these studies can safely be pooled. Another limitation is that in some studies, a considerable number of participants had a previous depressive episode. One could argue that these interventions can better be considered prevention of recurrence. However, most of the studies reporting the proportion of participants with previous episodes indicated that this proportion was lower than 50%, indicating that for at least a large part of participants prevention was focused on their first episode. Third, the control condition in the majority of the included studies was care-as-usual. This implies that the comparison cannot pinpoint the specific efficacy of these interventions but may reflect only additional attention given to the intervention group. However, one can also argue that we are particularly interested in this effect in order to decide whether an intervention should be added to current standard practices. The final limitation is the short follow-up periods. Only a handful of studies reported follow-up longer than 2 years. It is possible that these interventions did not actually prevent the onset of disorders, but only delayed it for some period of time. It should be noted, however, that delaying major depressive episodes during a critical period could have important positive effects. For example, preventing postpartum depression would not only benefit the mother, but would also prevent the sequelae of maternal depression as the infant develops. Similarly, if adolescent depression could be delayed for even a few years,

Table 3
Subgroup analyses.

Subgroups	Categories	N _{comp}	RR	95% CI	I ²	95% CI	p
• Prevention type	→ Indicated	33	0.81	0.70–0.94	22	0–49	0.72
	→ Selective	16	0.79	0.64–0.99	56	23–75	
	→ Universal	1	1.12	0.50–2.53	–	–	
• Age groups	→ Children/adolescents	14	0.71	0.51–0.99	25	0–60	0.48
	→ Adults	25	0.81	0.71–0.93	33	0–59	
	→ Older adults	11	0.91	0.68–1.22	56	14–78	
• Target group	→ Perinatal depression	9	0.73	0.52–1.00	55	5–79	0.31
	→ General medical	11	0.71	0.55–0.93	12	0–53	
	→ College students	5	0.93	0.65–1.31	0	0–75	
• Intervention	→ Other	25	0.87	0.74–1.03	34	0–59	0.47
	→ CBT	22	0.81	0.67–0.98	37	2–62	
	→ IPT	8	0.61	0.37–1.00	8	0–70	
• Format	→ Stepped care	5	0.87	0.58–1.30	55	0–83	0.81
	→ Other	15	0.87	0.72–1.04	37	0–66	
	→ Individual	16	0.77	0.62–0.96	47	6–71	
• Control group	→ Group	19	0.84	0.67–1.05	32	0–61	0.25
	→ Other/mixed	15	0.83	0.68–1.00	22	0–57	
	→ Care-as-usual	37	0.84	0.74–0.96	43	15–61	
• Country	→ Other	13	0.72	0.56–0.93	9	0–48	0.001
	→ US	26	0.72	0.61–0.86	29	0–56	
	→ Europe	17	0.83	0.68–1.00	43	0–68	
• Risk of bias	→ Other	7	1.06	0.90–1.24	0	0–48	0.08
	→ Low	22	0.86	0.73–1.02	45	9–67	
	→ Moderate	16	0.68	0.57–0.81	0	0–48	
	→ High	12	0.90	0.63–1.29	6	0–61	

Table 4
Multivariate meta-regression analyses.

Subgroups	Categories	Coeff	SE	p
• Indicated vs other types of prevention		-0.02	0.22	0.92
• Follow-up (in months; continuous)		-0.00	0.01	0.89
• Age groups	→ Children/adolescents	Ref.		
	→ Adults	-0.18	0.26	0.48
	→ Older adults	0.32	0.32	0.32
• Target group	→ Perinatal depression	0.11	0.34	0.74
	→ General medical	-0.06	0.33	0.85
	→ College students	0.38	0.41	0.35
	→ Other	Ref.		
• CBT vs other interventions		-0.18	0.20	0.38
• Format	→ Individual	Ref.		
	→ Group	0.11	0.30	0.72
	→ Other/mixed	0.18	0.29	0.54
• Country	→ US	Ref.		
	→ Europe	0.26	0.23	0.26
	→ Other country	0.41	0.27	0.13
• CAU vs other control group		0.31	0.26	0.24
• Risk of bias	→ (continuous)	-0.07	0.07	0.36
• Intercept		-0.53	0.58	0.37

young people might be able to successfully navigate key transitions, such as graduation from secondary school, completing higher education, or starting a career. Having these resources under their belt could reduce the impact of clinical depression if they develop an episode later on.

Despite the limitations mentioned above we can conclude that

Appendix A. Full search string for PubMed

A.1. Search string for the main database of randomized trials on psychological interventions for depression

(Psychotherapy [MH] OR psychotherap*[All Fields] OR cbt[All Fields] OR "behavior therapies"[All Fields] OR "behavior therapy"[All Fields] OR "behavior therapeutic"[All Fields] OR "behavior therapeutical"[All Fields] OR "behavior therapeutics"[All Fields] OR "behavior therapist"[All Fields] OR "behavior therapists"[All Fields] OR "behavior treatment"[All Fields] OR "behavior treatments"[All Fields] OR "behaviors therapies"[All Fields] OR "behaviors therapy"[All Fields] OR "behaviors therapeutics"[All Fields] OR "behaviors therapeutic"[All Fields] OR "behaviors therapeutical"[All Fields] OR "behaviors therapist"[All Fields] OR "behaviors therapists"[All Fields] OR "behaviors treatment"[All Fields] OR "behaviors treatments"[All Fields] OR "behavioral therapies"[All Fields] OR "behavioral therapy"[All Fields] OR "behavioral therapeutics"[All Fields] OR "behavioral therapeutic"[All Fields] OR "behavioral therapeutical"[All Fields] OR "behavioral therapist"[All Fields] OR "behavioral therapists"[All Fields] OR "behavioral treatment"[All Fields] OR "behavioral treatments"[All Fields] OR "behavioural therapies"[All Fields] OR "behavioural therapy"[All Fields] OR "behavioural therapeutics"[All Fields] OR "behavioural therapeutic"[All Fields] OR "behavioural therapeutical"[All Fields] OR "behavioural therapist"[All Fields] OR "behavioural therapists"[All Fields] OR "behavioural treatment"[All Fields] OR "behavioural treatments"[All Fields] OR "behaviours therapies"[All Fields] OR "behaviours therapy"[All Fields] OR "behaviours therapeutics"[All Fields] OR "behaviours therapeutic"[All Fields] OR "behaviours therapeutical"[All Fields] OR "behaviours therapist"[All Fields] OR "behaviours therapists"[All Fields] OR "behaviours treatment"[All Fields] OR "behaviours treatments"[All Fields] OR "behavioural therapies"[All Fields] OR "behavioural therapy"[All Fields] OR "behavioural therapeutics"[All Fields] OR "behavioural therapeutic"[All Fields] OR "behavioural therapeutical"[All Fields] OR "behavioural therapist"[All Fields] OR "behavioural therapists"[All Fields] OR "behavioural treatment"[All Fields] OR "behavioural treatments"[All Fields] OR "behavioural therapist"[All Fields] OR "behavioural therapists"[All Fields] OR "behavioural treatment"[All Fields] OR "behavioural treatments"[All Fields] OR "cognition therapies"[All Fields] OR "cognition therapie"[All Fields] OR "cognition therapy"[All Fields] OR "cognition therapeutical"[All Fields] OR "cognition therapeutic"[All Fields] OR "cognition therapeutics"[All Fields] OR "cognition therapist"[All Fields] OR "cognition therapists"[All Fields] OR "cognition treatment"[All Fields] OR "cognition treatments"[All Fields] OR psychodynamic[All Fields] OR Psychoanalysis[MH] OR psychoanalysis[All Fields] OR psychoanalytic*[All Fields] OR counselling[All Fields] OR counseling[All Fields] OR Counseling[MH] OR "problem-solving"[All Fields] OR mindfulness[All Fields] OR (acceptance[All Fields] AND commitment[All Fields]) OR "assertiveness training"[All Fields] OR "behavior activation"[All Fields] OR "behaviors activation"[All Fields] OR "behavioral activation"[All Fields] OR "cognitive therapies"[All Fields] OR "cognitive therapy"[All Fields] OR "cognitive therapeutic"[All Fields] OR "cognitive therapeutics"[All Fields] OR "cognitive therapeutical"[All Fields] OR "cognitive therapist"[All Fields] OR "cognitive therapists"[All Fields] OR "cognitive treatment"[All Fields] OR "cognitive treatments"[All Fields] OR "cognitive restructuring"[All Fields] OR ("compassion-focused"[All Fields] OR "compassion-focussed"[All Fields]) AND (therapy[SH] OR therapies[All Fields] OR therapy[All Fields] OR therapie*[All Fields] OR therapis*[All Fields] OR Therapeutics [OR treatment*[All Fields]]) OR ((therapy[SH] OR therapies[All Fields] OR therapy [All Fields] OR therapie*[All Fields] OR therapis*[All Fields] OR Therapeutics[MH] OR treatment*[All Fields]) AND constructivist*[All Fields]) OR "metacognitive therapies"[All Fields] OR "metacognitive therapy"[All Fields] OR "metacognitive therapeutic"[All Fields] OR "metacognitive therapeutics"[All Fields] OR "metacognitive therapeutical"[All Fields] OR "metacognitive therapist"[All Fields] OR "metacognitive therapists"[All Fields] OR "metacognitive treatment"[All Fields] OR "metacognitive treatments"[All Fields] OR "meta-cognitive

prevention may indeed be an effective approach to reduce the disease burden of depression for individuals, their families, and societies. Considering the huge disease burden of depression, prevention interventions should be considered a viable option by clinicians and policy makers for people experiencing subthreshold symptoms of depression, clinicians and policy makers.

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Contributors

PC, RFM, SQ, and EK contributed to the conception of the study, BSP, EK, PC, CAF AND JL conducted the searches, PC and EK conducted the data extraction, PC conducted the analyses and wrote the first draft of the study, all authors revised the paper critically for important intellectual content and approved the final version of the manuscript.

Declaration of competing interest

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therapies"[All Fields] OR "meta-cognitive therapy"[All Fields] OR "meta-cognitive therapeutic"[All Fields] OR "meta-cognitive therapeutics"[All Fields] OR "meta-cognitive therapeutical"[All Fields] OR "meta-cognitive therapist"[All Fields] OR "meta-cognitive therapists"[All Fields] OR "meta-cognitive treatment"[All Fields] OR "meta-cognitive treatments"[All Fields] OR "solution-focused therapies"[All Fields] OR "solution-focused therapy"[All Fields] OR "solution-focused therapeutic"[All Fields] OR "solution-focused therapeutics"[All Fields] OR "solution-focused therapeutical"[All Fields] OR "solution focused therapies"[All Fields] OR "solution focused therapy"[All Fields] OR "solution focused therapeutic"[All Fields] OR "solution focused therapeutics"[All Fields] OR "solution focused therapeutical"[All Fields] OR "solution-focussed therapies"[All Fields] OR "solution-focussed therapy"[All Fields] OR "solution-focussed therapeutic"[All Fields] OR "solution-focussed therapeutics"[All Fields] OR "solution-focussed therapeutical"[All Fields] OR "solution focussed therapeutic"[All Fields] OR "solution focussed therapeutics"[All Fields] OR "solution focussed therapeutical"[All Fields] OR "self-control therapies"[All Fields] OR "self-control therapy"[All Fields] OR "self-control therapeutics"[All Fields] OR "self-control therapeutical"[All Fields] OR "self-control therapeutic"[All Fields] OR "self-control training"[All Fields] OR "self-control trainings"[All Fields] OR "self control therapies"[All Fields] OR "self control therapy"[All Fields] OR "self control therapeutics"[All Fields] OR "self control therapeutical"[All Fields] OR "self control therapeutic"[All Fields] OR "self control training"[All Fields] OR "self control trainings"[All Fields] AND (Depressive Disorder[MH] OR Depression[MH] OR dysthymi*[All Fields] OR "affective disorder"[All Fields] OR "affective disorders"[All Fields] OR "mood disorder"[All Fields] OR "mood disorders"[All Fields] OR depression*[All Fields] OR depressive*[All Fields] OR "dysthymic disorder"[MeSH Terms]) AND ((randomized controlled trial [pt] OR controlled clinical trial [pt] OR randomized [tiab] OR randomly [tiab] NOT (animals[mh] NOT (animals[mh] AND humans [mh])))

A.2. Search string for additional searches for universal and selective prevention

The full search string for PubMed for these additional searches is: (("depressive disorder"[MeSH Terms] OR ("depressive"[All Fields] AND "disorder"[All Fields]) OR "depressive disorder"[All Fields] OR "depression"[All Fields] OR "depression"[MeSH Terms]) OR depressive[All Fields]) AND (("prevention and control"[Subheading] OR ("prevention"[All Fields] AND "control"[All Fields]) OR "prevention and control"[All Fields] OR "prevention"[All Fields]) OR preventive[All Fields]) AND Randomized Controlled Trial[ptyp]

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B.1. References of primary studies

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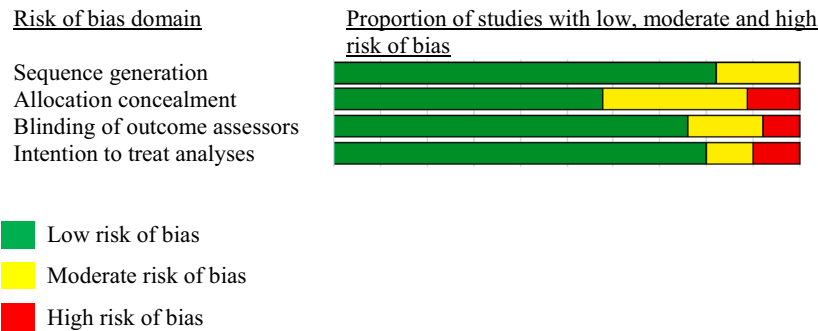
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Appendix C. Risk of bias in the included studies



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