Chapter 2

Are interventions for depression prevention effective? A meta-analysis

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Preventing the onset of major depressive disorder:
a meta-analytic review of psychological interventions.

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Abstract

Background

Depressive disorders are highly prevalent, have a detrimental impact on the quality of life of patients and their relatives and are associated with increased mortality rates, high levels of service use and substantial economic costs. Current treatments are estimated to only reduce about one-third of the disease burden of depressive disorders. Prevention may be an alternative strategy to further reduce the disease burden of depression.

Methods

We conducted a meta-analysis of randomized controlled trials examining the effects of preventive interventions in participants with no diagnosed depression at baseline on the incidence of diagnosed depressive disorders at follow-up. We identified 32 studies that met our inclusion criteria.

Results

We found that the relative risk of developing a depressive disorder was incidence rate ratio 0.79 (95% CI 0.69 - 0.91), indicating a 21% decrease in incidence in prevention groups in comparison with control groups. Heterogeneity was low (I^2 = 24%). The number needed to treat (NNT) to prevent one new case of depressive disorder was 20. Sensitivity analyses revealed no differences between type of prevention (e.g. selective, indicated or universal) nor between type of intervention (e.g. cognitive behavioural therapy, interpersonal psychotherapy or other). However, data on NNT did show differences.

Conclusions

Prevention of depression seems feasible and may, in addition to treatment, be an effective way to delay or prevent the onset of depressive disorders. Preventing or delaying these disorders may contribute to the further reduction of the disease burden and the economic costs associated with depressive disorders.

Introduction

About 150 million people worldwide are affected with depression at any moment in time, and one in every five women and 1 in every eight men experience an episode of major depression over the course of their life (1-3).

Depression is a major factor in quality of life decrements and is also associated with premature death (4). People suffering from depressive disorders experience substantial loss in quality of life (5). Between 1990 and 2010, major depression moved up from 15th to 11th in terms of global disease burden measured in disability-adjusted life years (DALYs) (6) and it is projected to become the single leading cause of disease burden by 2030 (7). Depressive disorders are associated with high levels of service use and economic costs stemming from productivity losses (8). Although effective treatments are available, it has been estimated that, even under optimal conditions, contemporary treatments can reduce only about one-third of the disease burden associated with major depressive disorder (MDD) (9, 10).

A way to further reduce the disease burden of major depression could be to reduce the influx of new cases that is, to reduce the incidence. This is done by prevention rather than treatment. Strengthening protective factors (e.g. social, cognitive or problem-solving skills) or alleviating prodromal disease stages (e.g. reducing severity of depressive symptoms) have been investigated in a considerable number of preventive studies (11-13). Several studies examining the effects of preventive interventions have found favourable effects on the incidence of new cases (14-20), but several others did not (21-24). Whether the effect of the currently available preventive interventions decays over time, indicating effectiveness only when a person is participating in the preventive intervention, is being investigated.

There are different types of prevention. Universal prevention focuses on the general public or a whole population group regardless of risk status. Selective prevention targets individuals or subgroups that are at higher risk of developing mental disorders than average individuals or subgroups. Indicated prevention focuses on individuals who are identified as having prodromal symptoms or biological markers to mental disorders, but who do not yet meet the diagnostic criteria for a full-blown diagnosis (25, 26). In a previous meta-analysis of studies examining the effects of preventive interventions on the incidence of new cases, we found an overall effect of universal, selective and indicated prevention on the incidence of depressive disorders (13). Universal prevention was only examined in two studies and it was therefore impossible to investigate effectiveness (21, 27). The studies included in that meta-analysis were conducted among various populations and the interventions differed considerably, which might have influenced the results.

One way to examine whether preventive interventions are effective is to look at the numbers needed to treat (NNT). The NNT indicates the number of people who would have to receive a preventive intervention in order to prevent one new case of depression. This leads to the expectation that NNT is inversely related to the a priori risk of the disorder (i.e. lower NNTs in indicated prevention).

In our earlier meta-analysis we could include 19 trials examining the effects of preventive interventions, whereas we identified 32 studies for the current meta-analysis, using even more stringent criteria for inclusion. It was therefore deemed opportune to update the earlier meta-analysis, thus allowing us to not only estimate the overall effects of preventive interventions with greater precision, but also to examine characteristics of the interventions and participants as moderators of outcome. In addition, the large number of included studies allows us to examine subfields of prevention in more detail and with greater statistical power, such as prevention of postpartum depression, prevention at schools and prevention of depression in people with somatic illnesses. Also, we focus on whether the effect of type of intervention decays over time, thereby investigating if type of intervention works as a protection or inoculation against new onsets of MDD.

Methods

Search strategies and selection of studies

We conducted a comprehensive search of the literature in bibliographical databases. All relevant articles published between 1966 and March 2012 were included. The searches of these databases were done by combining terms indicative of prevention and depression. We specified the search for both MeSH terms and free-text words, but limiting the search to effectiveness studies (e.g. randomized trials, controlled trials, clinical trials). Furthermore, we examined the references of relevant previous meta-analyses and reviews and we reviewed the reference lists of retrieved articles.

Studies were included when they used a pretest- posttest randomized controlled design and examined the effects of a preventive, psychological intervention on the incidence of new cases of depressive disorders compared with a control group. Prevention was defined as reducing the incidence of new cases of MDD. Therefore, we selected studies where participants did not meet the diagnostic criteria (according to the DSM-III-R or DSM-IV) at baseline and were 'at risk' of becoming depressed at follow-up as assessed with a diagnostic instrument. We also included studies examining universal, selective and indicated prevention (28). Studies focusing on preventing depressive disorders after a specific live event (e.g. postnatal depression) were

also included. A study was excluded when the participants were receiving a treatment for another mental disorder. Also studies on maintenance treatment or relapse prevention were excluded.

Quality assessment

We used four basic criteria of the 'risk of bias' tool to assess possible sources of bias (29): sequence generation (the method used to generate the allocation sequence is described in sufficient detail to allow an assessment of whether it should produce comparable groups); allocation concealment (the method used to conceal allocation is described in sufficient detail to see whether intervention allocations were foreseeable in advance of, or during enrolment); blinding of outcome assessors (all measures used to blind personnel as well as study participants to knowledge of which intervention participants were allocated); and incomplete outcome data (methods described whether all randomized participants were used in the analyses). The quality assessment was conducted independently by two reviewers (PC and KvZ). Disagreements were solved by consensus.

Analyses

We used the Comprehensive Meta-Analysis Software package, version 2.2.021 (Biostat, Englewood, NJ) for all analyses. First we calculated the incidence rate ratio (IRR) for developing a depressive disorder in the intervention compared with the control group for each study. Then we calculated the pooled mean of the IRRs. We investigated both the fixed and the random-effects model (29). The random-effects model assumes that the included studies are drawn from 'populations' of studies that may differ from each other and we feel this is more appropriate to the current study. The effect sizes resulting from included studies are allowed to differ under this model, not only because of the sample error of each study, but also due to true (systematic) variation across studies. We also calculated the NNT. This indicates how many people would have to receive a preventive intervention in order to prevent one new case of depression. The NNT was calculated as the inverse of the pooled absolute risk difference.

As a test of homogeneity of effect sizes, we calculated the I^2-statistic, which is an indicator of heterogeneity. The I^2-statistic (30) can be expressed as a percentage, where a value of 0% indicates no heterogeneity, and 25%, 50% and 75% can be interpreted as low, moderate and high levels of heterogeneity (31). We calculated 95% confidence intervals (CIs) around I^2, using the non-central chi-square-based approach within the heterogeneity command in Stata (32). We also calculated the Q-statistic and tested the level of significance.

Subgroup and meta-regression analyses were conducted according to the procedures implemented in the Comprehensive-Meta-Analysis software. We used mixed-effects analyses,

which pooled studies within subgroups with the random-effects model but tested for differences between subgroup with the fixed-effects model.

Publication bias was tested by inspecting the funnel plot on the primary outcome measure and by Duval and Tweedie's trim-and-fill procedure (33), which yields an estimate of the effect size after the publication bias has been taken into account (again, as implemented in the Comprehensive Meta-Analysis program). Also, we performed Egger's test.

Results

Searches and inclusion of studies

The literature search resulted in a total of 7447 articles found in PubMed (n = 2006), Cochrane Central Register of Controlled Trials (n = 2707), PsychInfo (n = 932) and EMBASE (n = 1802). We removed duplicates, leaving 4591 articles to be examined. We retrieved a total of 235 full-text articles that potentially met our inclusion criteria. Of these, 203 were excluded. Most (n = 135) were excluded because they lacked a diagnosis at the baseline and/or the follow up. Another reason for not including studies was lack of randomization (n = 18). All reasons for exclusion are noted in Figure 1. Control groups primarily consisted of care as usual, with some exceptions such as: placebo pill, booklet or no intervention (Table 1).

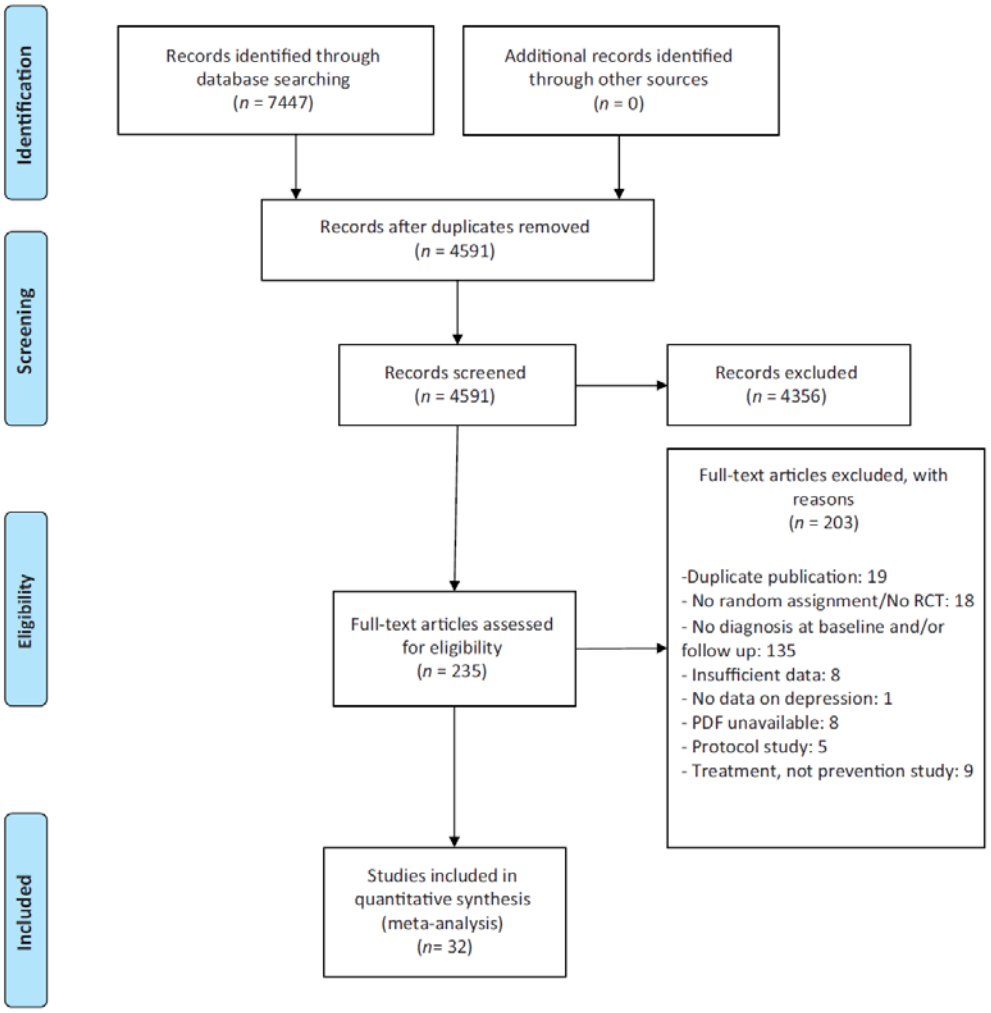

Figure 1. Flow chart of included studies

Characteristics of included studies

A total of 32 studies with 6214 participants (3312 in the prevention groups and 2902 in the control groups) met all inclusion criteria (14-21, 23, 24, 27, 34-57). In one study three different intervention groups were examined (27) so we were able to include 34 comparisons between preventive interventions and control groups. Table 1 shows selected characteristics of the included studies. Sheffield et al. (2006) investigated a universal preventive intervention and two indicated preventive interventions. One other study examined universal prevention, whereas

indicated prevention and selected prevention were each investigated by 15 other studies. The majority of studies (n = 21) focused on preventing MDD, 9 studies aimed at postpartum depression (PMDD) and 4 dealt with mood mixed disorder (i.e., a combination of MDD, dysthymia and/or minor depression). These were diagnosed by diagnostic instruments, such as the Structured Clinical Interview for DSM-IV (SCID) (Table 1), which use DSM-III-R or DSM-IV criteria. Most studies did not inform whether they excluded or included participants with a history of depressive disorders (n = 20). Four studies reported using participants with first episode of depression. Eight studies reported including participants with a history of depression, however participants did not experience a depressive disorder at the time of the baseline measure. Eight studies focused on adults in general, 1 study focused on adults with diabetes, 6 studies on pregnant women and 3 studies on (new) mothers, but most studies focused on adolescents or students (n = 14). Fifteen interventions were based on the principle of cognitive behavioural therapy. Some studies based their intervention on other psychological approaches, such as problem-solving therapy (n = 2) or interpersonal group therapy (n=5). The number of sessions ranged from 4 to 15. Most studies used interventions which consisted of 12 sessions (n = 7), 2 studies used preventive interventions which consisted of 4 sessions and 2 studies used preventive interventions consisting of 15 sessions. Eleven studies were conducted in Europe, 14 in the USA and 9 elsewhere. The follow-up periods of these studies varied between 2 and 60 months (median 9 months). Only one study reported a follow-up of 5 years and one study reported a follow-up of 36 months. One study reported a follow-up period of 2 months and 8 studies reported a follow-up period of 3 months. Most studies, however, also reported a follow-up period of 6 or 12 months (n = 28). Drop-out rates in the studies varied between 2% and 64%. Intention- to-treat-analyses were done by most studies (n = 19).

Quality of the articles was relatively high. Quality of studies was assessed on four criteria: allocation concealment, incomplete outcome data, blinding of out- come assessors, and sequence generation. Sixteen studies reported that blinding of the allocation of interventions was done adequately. Eight studies met all four criteria, 18 studies met two or three criteria and six studies met no or only one criterion.

Table 1. Selected characteristics of studies examining the effects of interventions on the incidence of depressive disorders

Study	Type	Recruitment	Target Population	Inclusion Criteria	Prevented Disorder	Conditions	N	Intervention	FU (mn)	Drop-out (%)	ITT
Allart et al. 2007 (34)	Ind	Community	Adults	BDI ≥10; no current MDD	MDD	1. CBT 2. CAU	61 41	12 CBT grp sessions	12	25	Y
Arnarson & Craighead, 2009 (15)	Ind	Screening at schools	Adolescents	CDI, CASQ ≥; no current DD	MDD	1. Eclectic 2. CAU	81 90	14 eclectic grp sessions	12	34	N
Austin et al. 2008 (24)	Sel	Antenatal clinics	Antenatal women	EPDS > 10; ANRQ > 23; hx of DD	Anxiety and PMDD	1. CBT 2. Booklet	191 86	6 CBT grp sessions + 1 booster	4	52	Y
Bot et al. 2010 (35)	Ind	outpatient clinics	People with diabetes	≥ 55 years; ≥ 16 CES-D	MDD	1. stepped care 2. CAU	58 56	12 weeks	24	36	N
Brugha et al. 2000 (36)	Sel	Screening	Primiparous women	Risk factor for depression	MDE	1. CBT 2. CAU	94 96	6 CBT + PST support grp sessions	3	9	N
Clarke et al. 1995 (37)	Ind	schools	Adolescents (15-16)	CES-D>24;no current MDD/DYS	MDD + Dysthymia	1. CBT 2. CAU	55 70	15 CBT grp sessions	12	27	N
Clarke et al. 2001 (14)	Ind	HMO	Adolescents (13-18)	CES-D > 24; ≥1 DSM-IV	MDD + Dysthymia	1. CBT 2. CAU	43 47	15 CBT grp sessions	24	17	N
Compas et al. 2009 (38)	Sel	Mental health clinics	Adolescents (9-15)	CESD/K-SADS-PL	MDE	1. CBT 2. Written info	56 53	12 sessions, four families each group	24	22	Y
De Jonge et al. 2009 (40)	Ind	Hospital	Patients with physical illness	CES-D, MINI	MDD	1. nursed-led 2. CAU	47 53	Supp couns or psych or a multi-disciplinary case conference	12	33	N
Elliott et al. 2000 (16)	Sel	Screening	Pregnant women	Vulnerable (LQ)	PMDD	1. PE 2. CAU	47 53	11 PE sessions + mutual support	3	15	Y

Table 1. Selected characteristics of studies examining the effects of interventions on the incidence of depressive disorders (continued)

Study	Type	Recruitment	Target Population	Inclusion Criteria	Prevented Disorder	Conditions	N	Intervention	FU (mn)	Drop-out (%)	ITT
Garber et al. 2009 (17)	Ind	Universities and health centres	Adolescent (13-17) of parents with depression	CESD > 20 and/or 2 mn remission from MDD or both	MDD	1. CBT 2. CAU	159 157	8 CBT grp sessions + 6 continuation sessions	9	9	N
Garcia et al. 2010 (41)	Sel	primary care	Primary care patients	18-65 yrs; SPPI no DSM-IV Axis	Somatoform disorders	1. psycho-education 2. no interven-tion	52 52	Five 120-min group sessions by family doctor	60	21	N
Gillham et al. 2006 (18)	Ind	Through HMO	Early adolescents (11-12)	CDI ≥ 7/9; no current MDD DYS	MDD, DYS	1. CBT 2. CAU	147 124	12 CBT grp sessions	24	41	Y
Hagan et al. 2004 (23)	Sel	neonatal unit	Mothers very preterm babies	No current DD	Postpartum depression	1. CBT 2. CAU	101 98	6 CBT grp sessions + PE	12	12	Y
Joling et al., 2012 (42)	Sel	Memory clinics, general practices, home care settings	Caregivers dementia patients	MINI	depressive or anxiety disorder	1. family meetings 2. CAU	96 96	6 in-person counseling meetings once every 2 to 3 months	12	26	y
Konnert et al. 2009 (43)	Ind	Residents of nursing homes	Nursing home residents (over 60)	No MDE, GDS ≥ 9	MDD	1. CBT 2. CAU	20 23	13 CBT sessions	6	33	N

Table 1. Selected characteristics of studies examining the effects of interventions on the incidence of depressive disorders (continued)

Study	Type	Recruitment	Target Population	Inclusion Criteria	Prevented Disorder	Conditions	N	Intervention	FU (mn)	Drop-out (%)	ITT
Lara et al. 2009 (44)	Ind	Hospital, clinic and community health care centre	Pregnant women in Mexico	CES-D ≥ 16 and/or self-report hx of MDD	MDD	1. CBT 2. CAU	250 127	8 PE grp sessions	4-9	64	Y
Martinovic et al. 2006 (45)	Sel	Community + clinic	Adolescents (13-19) with epilepsy	sD; no current DD	MDD	1. CBT 2. CAU	15 15	12 CBT grp sessions	9	6	N
Muñoz et al. 1995 (46)	Sel	GP records	GP patients	No MDD in past 6 mn	MDD, dysthymia	1. CBT 2. CAU	72 78	8 CBT grp sessions (CWD)	12	8	N
Muñoz et al. 2007 (47)	Ind	Screening	Pregnant Latina women	CES-D ≥ 16; hx of MDD	PMDD	1. CBT 2. CAU	21 20	12 CBT grp sessions (CWD)	12	9	N
Robinson et al. 2008 (48)	Sel	Community, universities & hospitals	Post-stroke patients	No current DD, HAM-D < 11; SCID	Poststroke depression	1. PST 2. Placebo	59 58	6 PST session + 6 booster sessions	12	9	y
Rovner et al. 2007 (49)	Sel	Screening in outpatient centers	Older patients	No current DD; SADS	MDD or minor depr.	1. PST 2. CAU	95 99	6 indv PST sessions	6	13	Y
Seligman et al. 1999 (50)	Sel	All new students	Undergraduate students	ASQ = bottom quartile, no current MDD	MDD	1. CBT 2. CAU	106 119	8 CBT grp sessions	36	4	N
Sheffield et al. 2006 (27)	Uni/ Ind	School	All students of 36 schools	High-symptom students, no MDD/DYS	MDD, dysthymia	1. CBT-Uni 2. CBT-Ind 3.CBT-Ind 4. CAU	107 100 110 125	8 CBT + 1 PST grp lessons	18	15	Y
Spence et al. 2003 (21)	Uni	School	Students of 18 schools	ADIS-C	Major depression	1. CBT 2. CAU	751 749	8 grp lessons of CBT + PST	12	15	N

Table 1. Selected characteristics of studies examining the effects of interventions on the incidence of depressive disorders (continued)

Study	Type	Recruitment	Target Population	Inclusion Criteria	Prevented Disorder	Conditions	N	Intervention	FU (mn)	Drop-out (%)	ITT
Van 't Veer-Tazelaar et al. 2009 (51)	Ind	PIKOproject	Older adults in primary care	No MDE;CES-D ≥16	MDD/ anxiety	1. CBT + PST 2. CAU	86 84	3 months CBT + nurse calls/visits, then 7 PST sessions	24	24	Y
Willemse et al. 2004 (53)	Ind	general practice	Adults (18-65)	One MDD core symptom, no MDD in past 6 mn (CIDI)	MDD, dysthymia	1. CBT 2. CAU	107 109	1 ftf contact + self-help book + 6 short telephone consultations (CWD)	12	37	Y
Young et al. 2006 (19)	Ind	school	Adolescents (15-16)	CES-D ≥ 16; 2 symptoms; no MDD/DYS	MDD, dysthymia (K-SADS)	1. IPT 2. CAU	27 14	2 indv + 8 IPT grp sessions	6	2	Y
Young et al. 2010 (55)	Ind	Two-stage screening	Adolescents (13-17)	CES-D 16 – 39; K-SADS-PI	MDD	1. IPT-AST 2. SC	36 21	1. 2 pre-grp sessions + 8 90-min grp sessions 2. 30-45 min indv counseling	18	23	Y
Zlotnick et al. 2001 (56)	Sel	hospitals	Pregnant women	≥1 risk indicators PDD, no MDD	PMDD	1. IPT 2. CAU	17 18	4 IPT grp sessions	3	5	N
Zlotnick et al. 2006 (20)	Sel	hospitals	Pregnant women	High score risk survey, no current MDD	PMDD (LIFE)	1. IPT 2. CAU	17 46	4 IPT grp sessions	3	13	N

Table 1. Selected characteristics of studies examining the effects of interventions on the incidence of depressive disorders (continued)

Study	Type	Recruitment	Target Population	Inclusion Criteria	Prevented Disorder	Conditions	N	Intervention	FU (mn)	Drop-out (%)	ITT
Zlotnick et al. 2011 (57)	Sel	Primary care clinics + private OBGYN clinic	Pregnant women (18-40yrs)	EPDS/SCID	MDD/PMDD	1. IPT 2. CAU	28 26	4 IPT + booster session	3	15	Y

Abbreviations: ADIS-C, Anxiety disorders interview schedule children; ANRQ, Antenatal Risk Questionnaire; BDI, Beck Depression Inventory, (C) ASQ, (Children's) Attributional Style Questionnaire; CAU, care as usual; CBT, cognitive behavioural therapy; CDI, Children's Depression Inventory; CES-D, Centre for Epidemiologic Studies-Depression Scale; CWD, Coping with depression; DAS, Dysfunctional Attitude Scale; DD, depressive disorder, DYS, dysthymia; EPDS, Edinburgh Postnatal Depression Scale; GDS, Geriatric Depression Scale; HAM-D, Hamilton rating scale Depression; HMO, Health Maintenance Program; hx, past history; IND, Indicated; IPT, Interpersonal therapy; K/SADS/PL, Kiddie-Sads-Present and Lifetime Version; LQ, Leverton Questionnaire; MDD, major depressive disorder; MDE, major depressive episode; MINI, Mini-International Neuropsychiatric Interview; mn, months; OBGYN, Obstetrics and gynaecology; PIKO, Prevention Intervention for Frail Elderly; PMDD, postpartum depression; PST, problem solving therapy; SADS, Schedule for Affective Disorders and Schizophrenia; SCID, Structured Clinical Interview for DSM-IV; sD, subthreshold depression; SEL, selective; SPPI, Standardized Polyvalent Psychiatric Interview; VAS, Visual Analogue Scale; Uni, universal.

Overall incidence rate ratios

We calculated the mean IRR by combining the IRRs at different follow-up times into a single estimate. When looking at the fixed-effects model, the IRR for all 34 comparisons from the 32 studies was 0.82 (95% confidence interval (CI) 0.73 - 0.91; p < .001). Focusing on the random-effects model, the IRR for all 34 comparisons from the 32 studies was 0.79 (95% CI 0.69 - 0.91; p < .001). Heterogeneity was low (I^2=24). Because the differences between the fixed- and the random-effects models were small, we only report the results for the random-effects model (Table 2 and Figure 2).

There was one study that compared three interventions with one control group (27). Since these comparisons were not independent from each other, we examined whether removal of these comparisons would increase heterogeneity. The overall analyses of 32 studies resulted in a mean IRR of 0.77 (95% CI 0.66 - 0.90; p = .005), with low heterogeneity (I^2 = 29%). This was comparable to the mean IRR found in the total sample.

Since the IRR could differ at varying follow-up periods, we conducted several sensitivity analyses. We examined the IRR for each follow-up period separately (<5 months; 6 months, 7 - 12 months, 513 months; Table 2). We also conducted a separate analysis in which we used only the last follow-up period reported in each study (0.78; 95% CI 0.68 - 0.89; p <.001; I^2 = 29), and another analysis with only the first follow-up period of each study (0.79; 95% CI 0.69 - 0.92; p = .002; I^2 = 29). As can be seen in Table 2, we found few indications that the outcomes differed very much from the IRR in which all follow-up periods were pooled.

We also conducted meta-regression analyses to see whether there was any effect decay over time. First, we examined the association between IRR and the first follow-up period reported in the study. We did not find an association between IRR and first follow-up period (the point estimate of the slope was 0.003; 95% CI 0.007 - 0.013), although there was a trend (p = .06) suggesting that the effects of the interventions are lower at longer follow-up periods (median: 7.5 months; range: 2 - 60 months). In the second meta-regression analysis we used the last follow-up period reported in the studies. Again, these results did not show an association between IRR and last- follow-up occasion (p = .06; the point estimate of the slope was 0.000; 95% CI 0.01 - 0.01), suggesting that the longer it takes before the last follow-up period, the lower the incidence of depression is (median 12; range 3 - 60 months).

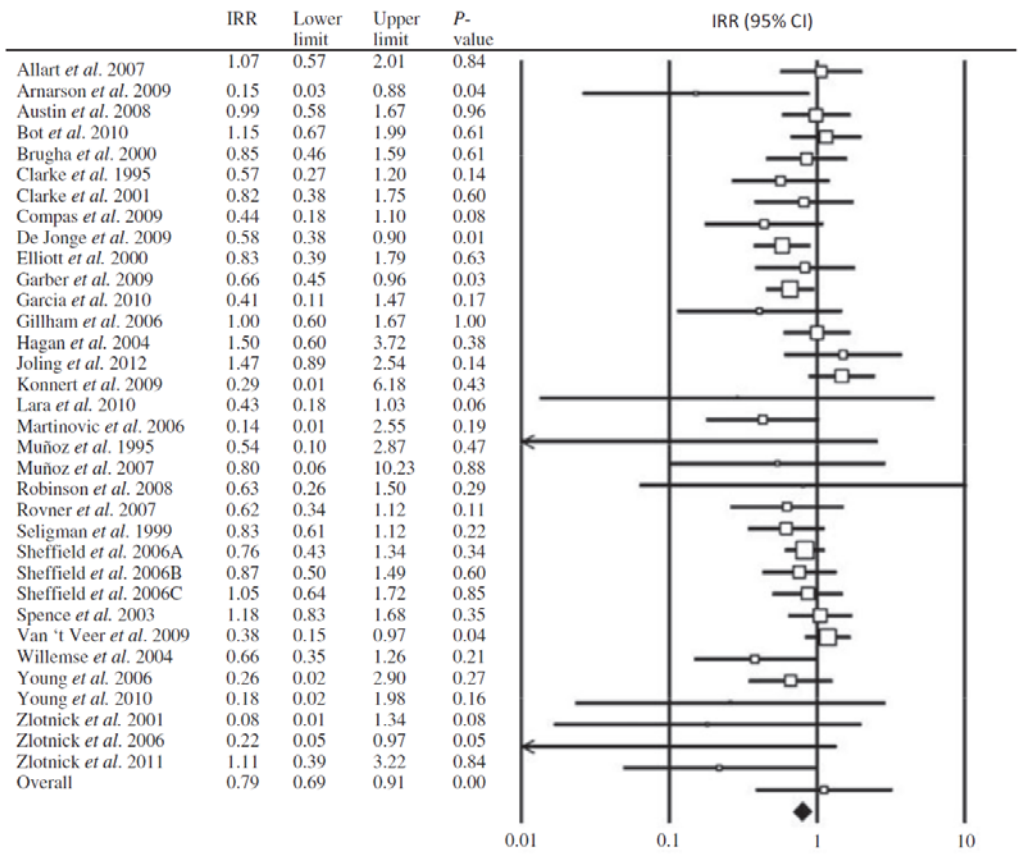

Figure 2. Effects of preventive interventions on the incidence of depressive disorders, incidence rate ratio (IRR) and number needed to treat. Lines represent IRR and 95% CI; the size of the square indicates the weight of each study

Table 2. Meta-analyses of studies examining the effects of preventive interventions on the incidence of depressive disorders: incidence rate ratio, heterogeneity, and numbers needed to treat at 2 months to 5 years

		N_{comp}	IRR	95% CI	I^2	95% CI	P [a)]	NNT	95% CI	P [a)]
Depressive disorders		34	0.79	0.69~0.91	24	0~50		20	13.33~37.04	
Sheffield excluded		31	0.77	0.66~0.90	29	0~54		16	11.11~30.30	
Only last follow up moment		34	0.78	0.68~0.89	29	0~53		17	11.90~30.30	
Only first follow up moment		34	0.79	0.69~0.92	29	0~54		21	13.89~45.45	
Follow up Period	<5 months	11	0.81	0.55~1.18	29	0~65		15	8.40~76.92	
	6	6	0.51	0.30~0.86	41	0~76		15	4.81~13.89	
	7-12	12	0.82	0.66~1.01	37	0~68		25	14.29~100	
	13-24	3	1.02	0.73~1.42	0	0~90		53	10.87~18.52	
	>24	2	0.77	0.52~1.16	10	[b)]		11	5.32~333.33	
Subgroup analyses										
Type of therapy	CBT	19	0.86	0.76~0.98	0	0~49	0.106	71	33.33~500	.003
	IPT	5	0.36	0.13~0.96	32	0~74		7	4.27~20.41	
	Other	10	0.68	0.49~0.95	52	1~77		12	7.14~37.04	
Outcome measure	MDD	21	0.79	0.69~0.92	13	0~48	0.766	21	13.51~50	.825
	PMDD	9	0.80	0.56~1.13	22	0~63		17	8.26~250	
	Mood mixed disorder	4	0.59	0.28~1.28	67	4~89		13	5.75~43.48	

Table 2. Meta-analyses of studies examining the effects of preventive interventions on the incidence of depressive disorders: incidence rate ratio, heterogeneity, and numbers needed to treat at 2 months to 5 years (continued)

		N_{comp}	IRR	95% CI	I^2	95% CI	P [a)]	NNT	95% CI	P [a)]
Age	Students	14	0.81	0.67~0.97	25	0~60	0.231	22	12.66~71.43	.419
	Adults	16	0.84	0.66~1.01	30	0~62		22	11.11~333.33	
	Elderly	4	0.55	0.36~0.85	0	0~85		11	6.80~32.26	
Target group	School-based	14	0.81	0.67~0.97	25	0~60	0.071	22	12.66~71.43	.108
	Perinatal depression	9	0.80	0.56~1.13	22	0~63		17	8.26~250	
	General Medical	10	0.70	0.56~0.87	0	0~62		16	10~37.04	
	Other	1	1.47	0.89~2.45	0	[b)]		11	37.04~4.65	
Prevention type	IND	17	0.74	0.62~0.89	14	0~51	0.414	14	9.43~23.26	.001
	SEL	15	0.81	0.64~1.02	26	0~60		20	11.11~100	
	UNI	2	1.01	0.66~1.53	41	[b)]			37.04~38.46	
Number of sessions	1-4	2	0.18	0.05~0.65	0	[b)]	0.024	5	2.58~18.52	.001
	5-9	16	0.88	0.75~1.04	20	0~56		53	23.26~250	
	10-12	10	0.87	0.67~1.13	0	0~62		19	9.71~200	
	13-18	5	0.63	0.47~0.85	0	0~79		9	6.29~18.87	

Table 2. Meta-analyses of studies examining the effects of preventive interventions on the incidence of depressive disorders: incidence rate ratio, heterogeneity, and numbers needed to treat at 2 months to 5 years (continued)

		N_{comp}	IRR	95% CI	I^2	95% CI	P [a)]	NNT	95% CI	P [a)]
Publication country	USA	14	0.67	0.54~0.82	0	0~55	0.051	13	8.93~25	.002
	Europe	11	0.77	0.57~1.04	47	0~73		16	8.62~90.91	
	Other	9	0.94	0.79~1.10	0	0~65		143	35.71~71.43	
Quality score	<3	12	0.79	0.59~1.06	53	10~76	0.894	14	7.87~71.43	.234
	3 or 4	22	0.77	0.67~0.90	0	0~46		29	18.52~71.43	

Abbreviations: CBT, cognitive behavioural therapy; IND, indicated prevention; IPT, interpersonal therapy; IRR, incidence rate ratio; I^2, heterogeneity; MDD, major depressive disorder; N, number of studies; NNT, number needed to treat; NR, not reported; PMDD, postpartum major depressive disorder; SEL, selective prevention; UNI, universal prevention.

[a]When subgroup included less than 3 studies analysis was done without that subgroup.

Publication bias

Inspection of the funnel plot (Figure 3) and Duval and Tweedie's trim-and-fill procedure attested to the possible presence of publication bias. After adjustment for publication bias, the effect size was increased from 0.82 to 0.86 (95% CI 0.74 - 1.00; number of trimmed studies: 10). The Egger's test also indicated an asymmetric funnel plot [intercept: 1.24, 95% CI 1.95 - 0.53, degree of freedom (df) 32, p =.001]. The fail-safe n was 175, indicating that 175 studies with an effect size of 0 would have to be included to not find a publication bias.

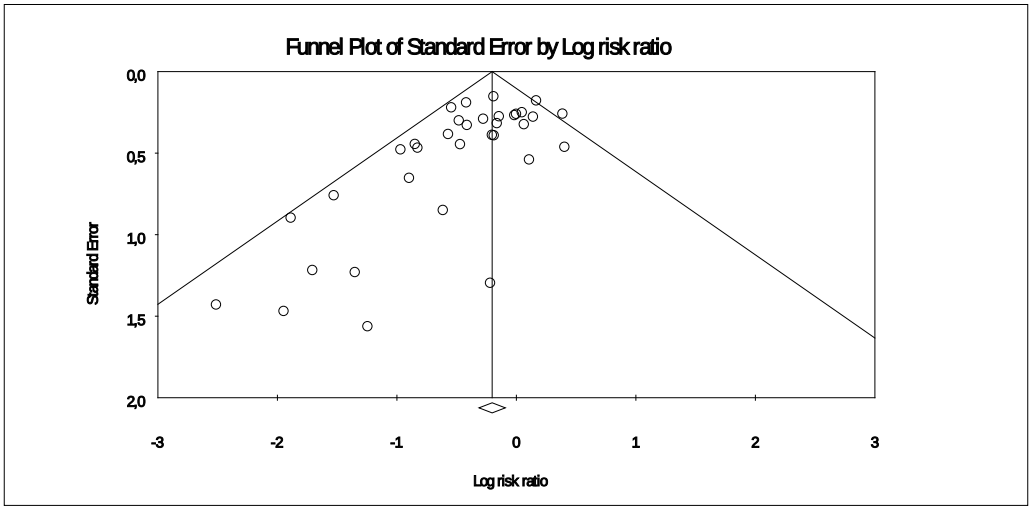

Figure 3. Funnel plot

Subgroup analyses

We conducted a series of subgroup analyses (Table 2). We examined whether the IRR differed according to type of prevention (indicated, universal or selective), type of intervention (CBT, IPT or other), age group (adolescent, adults or elderly), number of sessions (1 - 7, 8 - 11, 512; one study did not report the number of intervention sessions), country of publication (USA, EU or other), and target group (school- based, general medical, perinatal or other). The IRR did not differ in any of the subgroups (Table 2). The difference between CBT and IPT interventions, found by Cuijpers et al. in 2008, could not be replicated in the current meta-analyses. This null finding might be caused by the low number of studies using IPT as an intervention (n=5). However, when looking at NNT, as indicated in Table 2, there was a difference between number

needed to treat of CBT (NNT = 71), IPT (NNT = 7) and other (NNT = 12) interventions (p = .003), suggesting that preventive interventions using IPT are more effective than preventive interventions using CBT. In most subgroup analyses the heterogeneity was low to moderate. No heterogeneity was found in several subgroups of studies: subgroups using CBT, those focusing on the elderly and those using a target population of general medical patients. Also, no heterogeneity was found in subgroups having 8 - 11 sessions, having a publication score of 3 or 4 or from studies not published in Europe.

Discussion

We examined whether preventive interventions are effective in reducing the incidence of MDD. Results showed that preventive interventions lowered the incidence of depression by 21%, compared with controls. This is in agreement with the results of the previous meta-analyses conducted by Cuijpers et al. in 2008 (13). A reduction in incidence of 21% can be considered clinically relevant. In the current meta-analysis, we only included studies that used diagnostic criteria at baseline and follow-up, to exclude cases of depression at baseline and assess diagnostic status at follow-up. Using these rigorous criteria and the relatively large number of trials, this meta-analysis offers more robust evidence on the impact of preventive interventions on the incidence of new depressions than any previous meta-analysis.

The current meta-analyses did not show IPT to be more effective than CBT. This is in contrast to the findings of our earlier meta-analyses. Examining the NNT, however, shows that IPT (NNT = 7) is more effective than CBT (NNT = 71). Furthermore, there is no overlap in the 95% confidence intervals, reinforcing our suggestion that IPT might have a greater prophylactic effect than CBT. This result is consistent with our results from the previous meta-analysis conducted in 2008. It should, however, be interpreted with caution, since the number of studies using IPT (n = 5) was considerably lower than the studies using CBT (n = 20). If IPT is indeed more effective, this might be related to the fact that this type of intervention focuses more directly on the current problems and high-risk situations. This might be exactly what people in high-risk situations or with subthreshold symptoms need.

Also, results did not suggest that indicated prevention (IRR = 0.74) was more effective than selective prevention (IRR = 0.81). However, only two studies investigated universal prevention and those were therefore excluded from analysis. This does not necessarily imply that universal intervention might not be effective in high-risk subgroups.

Rose (58) proposed that there are two strategies to prevention: a population strategy of prevention, which targets a whole population regardless of individual differences in risk

status; and an individual strategy of prevention, which targets individuals at high risk for an adverse health outcome (59). Our meta-analysis is mainly focused on individual prevention. If we used less rigorous inclusion criteria (e.g. no diagnostic instrument to determine whether participants have a diagnosis), we might find results similar to another meta-analysis conducted in 2012 (60). This analysis found a beneficial effect in the prevention of postpartum depression in a range of interventions, individually based as well as multiple contacts. This shows that population-based strategies for prevention are interesting from a public health point of view and have the potential of reducing the incidence of depression considerably. However, our study also makes clear that there are no studies yet that show that population-based strategies actually reduce the incidence of depressive disorders.

Although prevention of depression seems to be effective, the NNT appears high (20 in the overall analysis), which is comparable to the NNT in the earlier analyses by Cuijpers (NNT = 22). There are, however, no normative thresholds for lower or higher NNT (13). Considering the impact depressive disorders have on social, economic and physical life and the clinical relevance, it seems an acceptable number. As discussed earlier, universal prevention might have a very different approach and yield very different results compared with selective and indicated prevention. Also, there were only two studies using universal prevention in this analysis. Therefore, it might be a consideration to not include universal prevention in other reviews like the current review. Other research did not show that the implemented intervention reduced the depressive symptoms in adolescents at high risk. The intervention was implemented in everyday life situations. The sample consisted of non-referred adolescents from the community. This study was, however, not included in the current meta-analysis because the researchers did not use a diagnostic instrument to diagnose depressive disorders at follow-up (61). However, the study shows that it is important to investigate the risk factors for depression, which could be due to premorbid vulnerability or due to the experience of previous episodes of depression. Future research should take history of depression into account.

Furthermore, the control/comparison groups in the included studies consisted mostly of treatments like care-as-usual or waiting-list. These are passive rather than active forms of 'treatments'. There is, therefore, no control for face-to-face time and attention. These are, however, nonspecific aspects of structured interventions like IPT or CBT. If future research included more active comparators, it would greatly improve the strength with which conclusions can be drawn about the specific prophylactic value of learning-based psychotherapies.

Most follow-up periods were between 6 and 12 months (n = 28); only 2 studies had follow-up periods beyond 2 years. Therefore, it is not clear whether preventive interventions actually prevented the incidence of depression or simply delayed the onset of depressive episodes. We performed analyses per follow-up (<5, 6, 7 - 12, ≥ 13 months). Comparing the

effects of preventive interventions and first follow-up months showed a small positive association, indicating that the more months pass, and the more effective the preventive intervention is. However, comparing the effects of preventive interventions and last follow-up period, this had a very small negative association. This might indicate that the effects of the preventive intervention became smaller over longer follow-up periods, suggesting that the preventive interventions delay the onset of disorders rather than preventing them altogether. However, only few studies had longer follow-up periods than 2 years. From a clinical point of view, preventing new onsets of depression would obviously be preferable since it would completely avoid the burden of disease in all prevented cases. However, delaying the onset is also important. Every year a disorder is delayed is a year without suffering.

We acknowledge several limitations of this study. First, several studies examined different populations and used different types of interventions. That said, according to the I^2 statistic, heterogeneity was low to moderate, indicating that it may be a fairly homogeneous set of studies. Second, the follow-up periods differed between studies. We therefore examined the various follow-up periods. However, we also conducted regression analysis with only the first follow-up occasion and regression analysis with only the last follow-up occasion to see whether there was any effect of decay over time. Third, the numbers of studies in some of the subgroup-analyses were rather small and show only correlations. Therefore, results should be interpreted with caution.

In conclusion, it is encouraging that we found positive effects of preventive interventions on the incidence of major depression, which are clinically relevant. Prevention of depressive disorders is possible, and may, in addition to treatment, be an important way to further reduce the burden of disease due to a very prevalent and disabling condition: depression.

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