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Preventive interventions in offspring of parents with mental illness: a systematic review and meta-analysis of randomized controlled trials

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Review Article

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Abstract

Children with parents suffering from a psychiatric disorder are at higher risk for developing a mental disorder themselves. This systematic review and meta-analysis of randomized controlled trials aims to evaluate the efficacy of psychosocial interventions to prevent negative mental health outcomes in the offspring of parents with mental illness. Eight electronic databases, grey literature and a journal hand-search identified 14 095 randomized controlled trials with no backward limit to June 2021. Outcomes in children included incidence of mental disorders (same or different from parental ones) and internalizing and externalizing symptoms at post-test, short-term and long-term follow-up. Relative risks and standardized mean differences (SMD) for symptom severity were generated using random-effect meta-analyses. Twenty trials were selected (pooled $n = 2689$ children). The main therapeutic approaches found were cognitive-behavioural therapy and psychoeducation. A significant effect of interventions on the incidence of mental disorders in children was found with a risk reduction of almost 50% [combined relative risk = 0.53, 95% confidence interval (CI) 0.34–0.84]. Interventions also had a small but significant effect on internalizing symptoms at post-test (SMD = −0.25, 95% CI −0.37 to −0.14) and short-term follow-up (−0.20, 95% CI −0.37 to −0.03). For externalizing symptoms, a decreasing slope was observed at post-test follow-up, without reaching the significance level (−0.11, 95% CI −0.27 to 0.04). Preventive interventions targeting the offspring of parents with mental disorders showed not only a significant reduction of the incidence of mental illness in children, but also a diminution of internalizing symptoms in the year following the intervention.

Introduction

Having a parent with mental disorders is a significant risk factor for developing a severe mental illness, which can be explained by genetic, environmental and psychosocial factors (Hosman, van Doesum, & van Santvoort, 2009; Mattejat & Remschmidt, 2008; Wille, Bettge, & Ravens-Sieberer, 2008). The mechanisms of this association are very complex and subtle, with strong interrelationships between genetic and environmental factors (Apter, Bobin, Genet, Gratier, & Devouche, 2017). In addition, the interactional pathways between the suffering parent and their child are often bidirectional (Dodge, Bates, & Pettit, 1990). The presence of a mental disorder in a parent may thus be associated with poorer attachment, negative parenting and even abuse (O'Donnell et al., 2015). In turn, the child's subsequent difficulties may worsen the parent's psychological suffering and mental disorder. Children of depressed parents are about three times more likely to develop anxiety disorders, major depression or substance use disorder (Weissman et al., 2006). A previous meta-analysis (Rasic, Hajek, Alda, & Uher, 2014) highlighted that one-third of children of parents suffering from a severe mental illness may develop psychiatric disorders by early adulthood. Offspring are also at greater risk of developing internalizing and externalizing symptoms (Connell & Goodman, 2002), relationship difficulties (Bella et al., 2011; Larsson, Knutsson-Medin, Sundelin, & Trost von Werder, 2000) and demonstrate lower academic competences (Hay et al., 2001). Moreover, these long-term outcomes and adverse consequences have been shown to lead to high direct and indirect costs (Prince et al., 2007). The impact of preventive interventions on these costs has been evaluated in some studies that have highlighted significant economic benefits (Arango et al., 2018; Knapp, McDaid, & Parsonage, 2011).

A previous meta-analysis (Siegenthaler, Munder, & Egger, 2012) focusing on the offspring of parents with mental disorders showed that preventive interventions decreased by 40%

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[combined relative risk of 0.60, 95% confidence interval (CI) 0.45–0.79] the risk of developing the same mental illness as the parents and led to a small but significant decrease of internalizing symptoms. A more recent meta-analysis (Thanhäuser, Lemmer, de Girolamo, & Christiansen, 2017), which focused on emotional and behavioural symptoms in children and adolescents, reported similar results for internalizing symptoms, and small effects on externalizing symptoms, reaching significance only at follow-up. However, these previous studies did not systematically refer in their inclusion process to international classifications such as the Diagnostic and Statistical Manual of Mental Disorders (DSM; American Psychiatric Association, 2013) or the International Classification of Disease (ICD; World Health Organization, 1992) for the diagnosis of parental mental disorders, and did not assess the incidence in the offspring of mental disorders different than the parental ones.

Despite mounting data supporting the efficacy of early preventive intervention in the offspring of individuals with mental illness, a gap still exists between evidence from research and public health policies. The limited interest of health authorities in mental health prevention can be partly explained by several factors (Arango et al., 2018): the lack of awareness of the substantial economic savings from preventive interventions, the stigma of this population and the need for an initial investment in the training of professionals (which is costly and often yield limited short-term beneficial return). An almost decade-old review of available preventive programs (Reupert et al., 2012) found that most of the interventions were based on psychosocial education, with the need for further research to establish the conditions that can improve children's outcomes. In addition, this study only focused on children aged 5–18 years, excluded parenting programs that did not involve children and did not screen out based on study quality.

Therefore, the aims of the present study are: (i) to review existing preventive interventions focusing on children and adolescents of mentally ill parents and evaluated by randomized controlled trials; and (ii) to perform a meta-analysis of their efficacy on children's outcomes in terms of incidence of mental disorders (same or different than the parental ones) and internalizing and externalizing symptoms.

Methods

A systematic review of the literature and a meta-analysis of randomized controlled trials of preventive interventions in the offspring of parents with mental illness were performed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines (Moher, Liberati, Tetzlaff, & Altman, 2009). The review protocol was developed in advance and registered within PROSPERO (#CRD42020170843).

Search methods

The eight following electronic databases were used to identify relevant published literature: MEDLINE, MEDLINE in-process, EMBASE, Cochrane Central Register of Controlled Trials (CENTRAL, Cochrane Library), Web of Science, PsycINFO, PsycArticles and ERIC. In addition to this systematic screening, an exploration of the grey literature was conducted using the OpenGrey database. Search strategies, based on a previous meta-analysis (Siegenthaler et al., 2012) and adapted to the other databases, are provided in online Supplement 1. Reference lists of the relevant articles were screened, as well as studies included in prior reviews and meta-analyses, and a hand-search of the *Journal of the American Academy of Child and Adolescent Psychiatry* was performed (1987–2021). All articles identified were included with no backward limit to 30 June 2021. No language restrictions were applied.

Selection criteria

For inclusion in this review and meta-analysis, studies had to meet the following criteria: (i) child and adolescent under 18 years old of parents with a diagnosis of mental illness as classified by the DSM or the ICD, including mood disorders, anxiety disorders, psychotic disorders or substance use disorders; (ii) intervention aimed at child, parents or both, from different theoretical underpinnings (cognitive and behavioural psychotherapy, family system therapy, skill-building techniques, etc.), compared to a control group (no intervention, treatment as usual or another intervention); (iii) outcomes in child included the incidence of mental disorders (same or different than the parental ones) and/or the severity of internalizing and externalizing symptoms, measured by standardized instruments (including self-reports, parent or expert reports, or structured interviews); (iv) randomized controlled trials.

Exclusion criteria were defined as follows: (i) child with a diagnosis of mental disorder at the time of inclusion, or child belonging to another high-risk group (like premature babies); (ii) parents with unclear diagnosis of mental illness or only at-risk for mental illness (i.e. vulnerable population); (iii) interventions reporting outcomes exclusively related to parent–child interaction; (iv) clinical trials other than randomized controlled trials and studies with insufficient power making it impossible to calculate a standardized mean difference (SMD).

Data extraction and quality appraisal

Two reviewers (AL and AR) independently performed database search and article screening using Zotero software (Corporation for Digital Scholarship, USA). Data from each included trial were extracted and coded independently using a data extraction form. Any disagreement was resolved by discussion with a third reviewer (JPR) to reach a consensus.

The coded variables included characteristics of studies (characteristics of participants, sample size, type of interventions and control groups, funding and target audiences, outcome measures and instruments used, follow-up time points) and necessary data to calculate the effect size.

When data were missing or to clarify some values, the study's authors were contacted for further information. Twelve authors were contacted, of whom only four replied (Clarke et al., 2001; Compas et al., 2015; Kelley & Fals-Stewart, 2002; Van Santvoort, Hosman, van Doesum, & Janssens, 2014). Three trials could not be included in our meta-analysis because either the design (Zhang, Slesnick, & Feng, 2018) or the available data (Murray, Cooper, Wilson, & Romaniuk, 2003; Van Santvoort et al., 2014) did not allow us to conduct our analysis.

The quality of included studies was evaluated by two reviewers independently (AR and AL), using the quality assessment tool QUALSYST, from the Standard Quality Assessment Criteria for Evaluating Primary Research Papers from a Variety of Fields (Kmet, Lee, & Cook, 2004; Table 1). The classification of methodological quality was determined based on percentage scores

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Table 1. QUALSYST 14-item checklist for quality assessment of included studies

Studies/criteria	1	2	3	4	5	6	7	8	9	10	11	12	13	14	Total (%)
Catalano et al. (1999); Haggerty et al. (2008) (USA)	+	+	+	+	+/–	+/–	–	+	+/–	+	+	+	+	+	82
Clarke et al. (2001) (USA)	+	+	+	+	+	+	–	+	+/–	+	+	+	+	+	89
Coiro et al. (2012) (USA)	+	+	+	+	+	+/–	–	+	+/–	+/–	+	+	+	+	82
Compas et al. (2009, 2010, 2011, 2015) (USA)	+	+	+	+	+	+	–	+	+	+	+	+	+	+	93
Forman et al. (2007) (Canada)	+	+	+	+	+	–	–	+	+/–	+	+/–	+	+	+	79
Garber et al. (2009); Beardslee et al. (2013); Brent et al. (2015) (USA)	+	+	+	+	+	+	–	+	+	+	+	+	+	+	93
Giannakopoulos et al. (2021) (Greece)	+	+	+	+	+/–	–	–	+	+/–	+	+	+	+	+	79
Ginsburg (2009); Ginsburg, Drake, Tein, Teetsel, and Riddle (2015, 2020); Pella et al. (2017) (USA)	+	+	+	+	+	+	–	+	+	+	+	+	+	+	93
Jones et al. (2017) (UK)	+	+	+	+	+	+	–	+	+/–	+	+	+/–	+	+	86
Kelley & Fals-Stewart (2002) (USA)	+	+	+	+	+/–	–	–	+	+/–	+	+/–	+	+	+	75
Lenze et al. (2020) (USA)	+	+	+	+	+	+	–	+	+/–	+	+	+	+	+	89
Van Doesum et al. (2008); Kersten-Alvarez et al. (2010) (The Netherlands)	+	+	+	+	+	+	+	+	+/–	+	+	+	+	+	96
Lam et al. (2008) (USA)	+	+	+/–	+	+/–	–	–	+	+/–	+/–	+/–	+/–	+/–	+	61
Murray et al. (2003) (UK)	+	+	+	+	+	+	–	+	+/–	+	+	+	+	+	89
Solantaus et al. (2010); Punamäki, Paavonen, Toikka, and Solantaus (2013) (Finland)	+	+	+	+	+	–	–	+	+/–	+	+	+	+	+	82
Stanger et al. (2011) (USA, China)	+	+	+/–	+	+/–	–	–	+	+/–	+	+	+	+	+	75
Stein et al. (2018) (UK)	+	+	+	+	+	+	–	+	+	+	+	+	+	+	93
Van Santvoort et al. (2014) (The Netherlands)	+	+	+	+	+	–	–	+	+	+	+	+	+	+	86
Verduyn et al. (2003) (UK)	+	+	+	+	+	+	–	+	+/–	+	+	+	+	+	89
Zhang et al. (2018) (USA)	+	+	+/–	+	+	–	–	+	+/–	+	+	+	+	+	79

(NA) not applied; (+) fulfilled; (+/–) partly fulfilled; (–) not fulfilled.
Criteria: 1: Question/objective sufficiently described?; 2: Study design evident and appropriate?; 3: Method of subject/comparison group selection or source of information/input variables described and appropriate?; 4: Subject (and comparison group, if applicable) characteristics sufficiently described?; 5: If interventional and random allocation was possible, was it described?; 6: If interventional and blinding of investigators was possible, was it reported?; 7: If interventional and blinding of subjects was possible, was it reported?; 8: Outcome and (if applicable) exposure measure(s) well defined and robust to measurement/misclassification bias? Means of assessment reported?; 9: Sample size appropriate?; 10: Analytic methods described/justified and appropriate?; 11: Some estimate of variance is reported for the main results?; 12: Controlled for confounding?; 13: Results reported in sufficient detail?; 14: Conclusions supported by the results?
Calculation of the summary score: summary score (%) = (total sum/total possible sum) × 100. Total sum = [number of (+) × 2] + [number of (+/–) × 1]. Total possible sum = 28 – [number of (NA) × 2].

and therefore identified strong quality (score > 80%), good quality (score = 70–79%), fair quality (score = 50–69%) and poor quality (score < 50%).

Statistical analyses

Characteristics of the included studies were summarized narratively. Meta-analyses were conducted to pool data using RevMan 5.4 (RevMan 5.4, The Nordic Cochrane Centre, The Cochrane Collaboration, Copenhagen, Denmark) and STATA 14 (Stata 14, StataCorp LP, College Station, TX, USA). Because there were some differences between included studies' characteristics, a random-effects model was chosen for the analysis.

Risk ratios (RR) were calculated with their 95% CIs to estimate the difference between groups in the incidence of mental disorders at post-intervention. The RR gives an indication of the likelihood of the onset of a mental illness in the experimental group compared to the control condition. Values between 0 and 1 indicate a positive effect of the intervention, whereas values >1 indicate a negative effect of the intervention.

For internalizing and externalizing symptoms, SMD and 95% CI were used as the effect measure using the inverse variance method (Higgins & Green, 2011). A negative effect represented an improvement (less emotional and behavioural symptoms), and effect sizes were interpreted as small 0.20–0.49, medium 0.50–0.79, and large 0.8 and higher (Cohen, 1988). The mean scores with their standard deviations were extracted separately for the active interventions and the control groups. When multiple scales were reported for the symptoms, Child Behaviour Checklist (CBCL; Achenbach, 1991) was favoured since it was the most widely used.

For the externalizing symptoms, the Eyberg Child Behaviour Inventory (ECBI; Eyberg & Pincus, 1999), which is a behaviour-specific instrument consisting of a list of 36 behaviours, was preferred to the Strengths and Difficulties Questionnaire (SDQ; Goodman, 2001), which is less specific and includes both emotional and behavioural difficulties. When the outcome was the functioning impairment, the specific scale used (Global Assessment of Functioning scale, GAF) was chosen (Clarke et al., 2001).

In two instances, when the outcome was a measure of depressive symptoms (Clarke et al., 2001; Garber et al., 2009), the predefined hierarchical ranking (Hazell, O'Connell, Heathcote, & Henry, 2002) was followed for inclusion in the meta-analysis: (i) Children's Depression Rating Scale (CDRS-R); (ii) Hamilton Depression Rating Scale (HAMD); (iii) Children's Depression Inventory (CDI); (iv) Centre for Epidemiological Studies Depression Scale (CES-D). For all measures, subscales of specific symptoms were always preferred over total scores.

Most of the trials reported multiple assessments at different follow-up times for the effects of preventive interventions. Therefore, continuous outcome variables (internalizing and externalizing symptoms) were clustered into three different time windows: post-intervention follow-up (0–4 months), short-term follow-up (5–12 months) and long-term follow-up (15–68 months). 'Post-intervention' was defined as the completion of the main intervention, excluding booster sessions. When trials reported more than one assessment within a time window, the datapoint closest in time to that of the other studies within that window was chosen to minimize heterogeneity.

Regarding dichotomous outcomes (incidence of mental disorders in children), only five trials reported data on this variable, which did not allow us to cluster data in different time windows. For this reason, we selected the time points that were most similar to each other between trials, which resulted in combining assessments from 6, 12 and 144-month follow-up.

The I^2 statistic and Cochran Q's χ^2 test were performed to assess the heterogeneity of the results between trials. For the interpretation of the I^2 statistics, which indicates the proportion of the total variation in the estimated effects caused by heterogeneity between trials rather than chance, the Cochrane Handbook for Systematic Review of Interventions (Higgins & Green, 2011) was used. Values of I^2 suggest low heterogeneity between 0% and 40%, moderate heterogeneity between 30% and 60%, substantial heterogeneity between 50% and 90% and considerable heterogeneity between 75% and 100%. For the χ^2 test, heterogeneity was statistically significant when the p value was <0.1 (Higgins & Green, 2011). Publication bias was assessed using funnel plots and Egger's tests.

When studies significantly differed from the others, particularly in terms of extreme follow-up points, sensitivity analyses were conducted to identify outliers. When outliers could not be identified to reduce heterogeneity, subgroup analyses were conducted to examine the effect of some variables on the outcomes. These variables included the type of interventions (family, children or parents-based interventions), the type of control groups (active or non-active), the age of children and parents' and children's symptoms at baseline (when >50% participants had symptoms at baseline, it was considered as a presence of symptoms). For the age of children, when the range was large in the studies, we took the mean age of the children included to classify them in the different subgroups (0–2, 3–12 or 13–18 years old). The first assessment time point after the intervention was selected for subgroup analyses.

Results

A total of 31 articles reporting data from 20 independent randomized controlled trials were included in the systematic review, of which 17 trials were included in the meta-analysis. The selection process is reported in Fig. 1.

Characteristics of studies

Sample sizes ranged from 30 to 316 children per study, with a total of $N = 2689$ randomized children and $N = 2523$ parents included in the narrative synthesis, 80.9% of whom were mothers. For our meta-analysis, a total of $N = 2081$ randomized children and $N = 1915$ parents were included. Parents were diagnosed with mood disorders in 13 trials, substance use disorders in five, anxiety disorders in one and multiple disorders in one trial. Further details on the characteristics of parents are provided in online Supplementary Table S1. Studies were published from 1999 to 2021. Eleven were performed in the USA, four in the UK, two in the Netherlands, one in Canada, one in Greece and one in Finland. No articles needed to be translated.

Study quality

Studies quality is reported in Table 1. The control group could be an active intervention, such as groups for parents (lecture, discussion or training sessions), or self-study of written information. In contrast, treatment as usual and waiting list were considered as non-active control groups. Fourteen studies had strong quality

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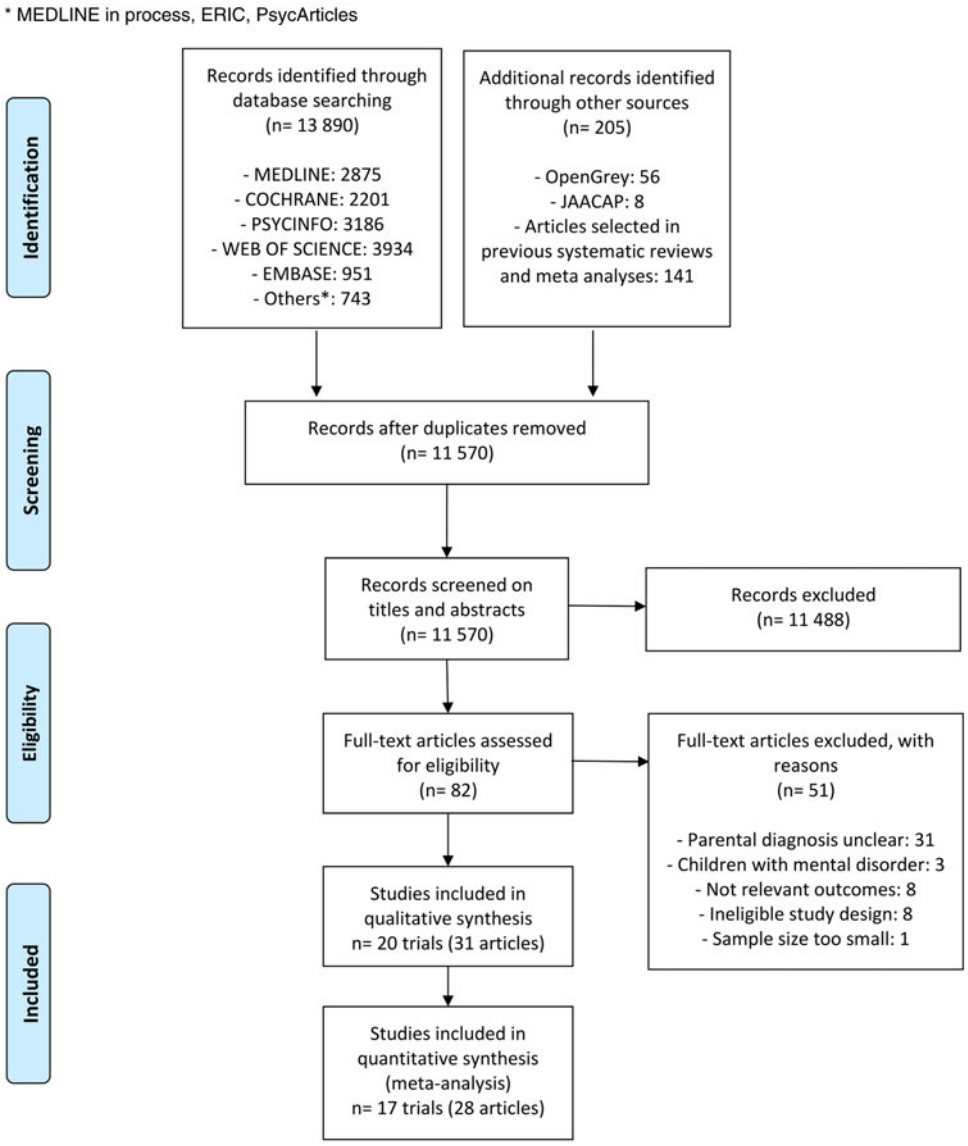

Fig. 1. Flow diagram of the selection process.

score, five studies good quality score and one study fair quality score. The quality criteria that differed the most between studies were the blinding of investigators, the description of the method used for randomization and the justification of an appropriate sample size.

Characteristics of interventions

Characteristics and main findings of each study are summarized in Table 2 and a detailed description of each intervention can be found in online Supplementary Table S2, based on the TIDieR (Template for Intervention Description and Replication) Checklist (Hoffmann et al., 2014). Preventive interventions were heterogeneous with respect to the age range of children included (from 4.5 months to 18 years old), their symptoms at baseline, the place (at clinic or at home) and the number and length of sessions (from 6 to 33 sessions, each lasting between 30 min and 2 h), the family members involved, and the type of control group used. Interventions focused on families (including the child and at least one of the two parents) in nine trials, on parents in four trials, on mothers only in four trials and on youth in three trials. Among the 11 studies reporting it, the average participation rate in the main sessions was 67.9%. The drop-out rate ranged from 4% (Clarke et al., 2001, at post-test) to 46% (Verduyn, Barrowclough, Roberts, Tarrier, & Harrington, 2003, in the control group at 12-month follow-up).

Cognitive-behavioural therapy (CBT)

Seven trials (Clarke et al., 2001; Coiro, Riley, Broitman, & Miranda, 2012; Compas et al., 2015; Garber et al., 2009; Kersten-Alvarez, Hosman, Riksen-Walraven, Van Doesum, & Hoefnagels, 2010; Murray et al., 2003; Verduyn et al., 2003) assessed intervention techniques mainly based on cognitive restructuring and behavioural therapy, among which three used formal treatment manuals. All these programs were designed for parents with mood disorders and focused either on youth, mothers or the whole family. In youth, the aims were to increase their understanding of parents' disorders, to identify and challenge negative thoughts and beliefs related to having a depressed parent, and to learn problem-solving skills. In parents, the aims were to improve parenting skills with behavioural training focused

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Table 2. Characteristics and main results of the 20 randomized controlled trials included in the systematic review

Study	Participants/ age	Parental disorder	Intervention	Control	Funding and target audiences	Outcomes	Main results and interpretation
Mood disorders							
Clarke et al. (2001) (USA)	*n* = 94 youth Age: 13–18 y-o *M* = 14.6 y-o	Major depression or dysthymia	YGBI Group Cognitive Therapy Prevention	Usual care	NIMH Grant (federal agency). Target: youth of families from the Health Maintenance Organization	Incidence of disorders: K-SADS-E Depressive symptoms: CES-D, CBCL-D, HAM-D Int/ext symptoms: CBCL	Significant effect in incidence of major depressive episode in experimental group at 12-month follow-up (9.3% *v.* 28.8%, *p* = 0.003). Persistence but diminution at 24-month follow-up. Significant effects in CES-D (−0.15) and HAM-D (−0.04)
Coiro et al. (2012) (USA)	*n* = 60 mother–child pairs Age: 4–11 y-o *M* = 6.4 y-o	Maternal major depression	MBI Medication group (paroxetine or bupropion) or Cognitive-Behavioural Therapy (CBT) group	Usual care (education + clinic appointment offered)	NIMH Grant (federal agency). Target: low-income women in the food subsidy program or family planning services	Int/ext symptoms: BSI of the BASC	No significant differences between groups. Modest significant improvement on BSI at 6 and 12-month follow-up among children with similar BSI at baseline whose mothers' depression was remitted (*t* = 2.08, df = 43, *p* = 0.04)
Compas et al. (2009, 2010, 2011, 2015) (USA)	*n* = 242 children *n* = 180 parents Age: 9–15 y-o *M* = 11.5 y-o	Major depression	FGBI Family group cognitive-behavioural intervention (FGCB)	Self-study written information (WI). Separate materials for parents and children	NIMH Grant (federal agency). Target: public health action	Incidence of disorders: K-SADS-PL Depressive/ anxiety symptoms: CES-D, YSR, CBCL-SS Int/ext symptoms: YSR, CBC-BS	Lower episode of MDD in FGCB (13.1% *v.* 26.3%, OR 2.37, 95% CI 1.05–5.35) from baseline to 24-month follow-up. Approach significance for any non-mood disorder. Significant effects on depressive, anxiety and int/ext symptoms maintained at long-term follow-up
Forman et al. (2007) (Canada)	*n* = 176 mother–child pairs *M* = 6.1 months	Post-partum major depressive episode	MBI Interpersonal Psychotherapy (IPT)	Waiting List Control (WLC): wait 12 weeks before receiving IPT Control group: non-depressed women	NIMH Grant and Traineeship (federal agency). Target: public health action	Int/ext symptoms: CBQ CBC/2–3	No significant effects on child outcomes. Post-partum depression treatment does not improve mothers' reports of child temperament and behaviour problems at 18-month follow-up

Garber et al. (2009); Beardslee et al. (2013); Brent et al. (2015) (USA)	*n* = 316 children *n* = 282 parents Age: 13–17 y-o *M* = 14.8 y-o	Major depression or dysthymia	YGBI Cognitive-Behavioural Prevention (CBP) group	Usual care alone	NIMH, National Center for Advancing Translational Sciences and Independent Scientist Awards Grant. Target: public health action (HMO, university medical centre, community) and education (schools).	Incidence of depression: DSR scale Depressive symptoms: CES-D CDRS-R	Significant lower incidence and duration of depressive symptoms during 0- to 9-month interval after intervention when index parent not depressed at baseline (significant moderator) in CBP group *v.* usual care (HR 0.54; $p = 0.003$). 6 years after the intervention, overall effects were maintained (not significant)
Giannakopoulos et al. (2021) (Greece)	*n* = 62 children *n* = 62 parents Age: 8–16 y-o *M* = 12 y-o	Major depressive disorder	FBI Family Talk Intervention (FTI): whole family group (individual and group sessions)	Control: Let's Talk about the Children (LTC) Parent-only group	Three-year funded mental health promotion program for children and young adolescents in Greece (Stavros Niarchos Foundation grants). Targets: decision makers, public health action	Depressive symptoms: CDI Anxiety symptoms: SCARED Int/ext symptoms: SDQ	No differences in child outcomes between groups but significant changes in both groups through the follow-up period. Improvement was faster in the FTI group as compared with the LTC. Change on parent's anxiety during follow-up was significantly associated with the respective changes on all child's outcome variables in both groups
Jones et al. (2017) (UK)	*n* = 97 families Age: 3–10 y-o	Bipolar disorder	PBI Integrated bipolar parenting intervention (IBPI): + TAU	Wait list control (WL) + TAU	Medical Research Council Grant. Target: public health action	Ext symptoms: SDQ ECBI	Significant improvement of SDQ at post-test in IBPI (−0.48 units per 4 weeks, $p = 0.01$), did not change at follow-up (after 16 weeks). No significant effect in ECBI
Lenze et al. (2020) (USA)	*n* = 42 mothers–child pairs Age: prenatal– 18 months	Major depression or dysthymia during pregnancy	FBI IPT-Dyad Interpersonal Psychotherapy for dyad	Enhanced TAU (ETAU) 30 telephone calls (questionnaires) during 9 months post-partum with 15 free diapers	NIMH grants. Target: public health action	Int/ext symptoms: ITSEA	No significant between-group differences in int/ext symptoms
Van Doesum et al. (2008); Kersten-Alvarez et al. (2010) (The Netherlands)	*n* = 58 mother–child pairs Age: up to 12 months	Mothers with post-partum major depressive	FBI Experimental group: mother–baby intervention	Control group: 3 telephone calls (general information, parenting advices) for 3 months	Grants from the Netherlands Organization for Health Research and Development,	Int/ext symptoms: CBCL (mothers) C-TRF (teachers)	No significant effect in int/ext symptoms. In families experienced many stressful life events:

(*Continued*)

Table 2. (*Continued.*)

Study	Participants/ age	Parental disorder	Intervention	Control	Funding and target audiences	Outcomes	Main results and interpretation
	M = 5.5 months	episode or dysthymia			the Foundation for Children's Welfare Stamps Netherlands and the Community Mental Health Center. Target: public health action		fewer mother-report externalizing symptoms in intervention group ($F = 4.75$, $p < 0.05$)
Murray et al. (2003) (UK)	*n* = 171 mother–baby pairs Age: under 4.5 months	Mothers with current post-partum major depressive disorder	MBI Cognitive-Behavioural Therapy group (CBT) Psychodynamic therapy group (PDT) Nondirective counselling group (NDC)	Control: routine primary care (TAU)	Birthright grant (non-profit organization) and Medical Research Council grant. Target: public health action	Int/ext symptoms: at 18 months: BSQ at 5 years: Rutter A[2] Scale PBCL	BSQ: significant improvement in NDC group compared to control at M8 ($\chi^2 = 12.19$, df = 1, $p = 0.001$). No significant benefit at 5 years post-partum
Solantaus et al. (2010); Punamäki et al. (2013) (Finland)	*n* = 145 children *n* = 109 families Age: 8–16 y-o	Current mood disorders	FBI Family Talk Intervention (FTI): whole family group	Control: Let's Talk about the Children (LTC) Parent-only group	Finnish Academy Grants. Target: public health action	Depressive symptoms: CDI, BDI Anxiety symptoms: SCARED Int/ext symptoms: SDQ	Significant improvement on anxiety symptoms ($p = 0.003$) and SDQ ($p = 0.0036$) in both groups (in the FTI from BL to 4 months, in the LTC from 4 to 18 months)
Stein et al. (2018) (UK)	*n* = 144 mother–child pairs Age at inclusion: 4.5–9 months	Mothers with persistent current major depressive disorder in post-partum	MBI Cognitive-Behavioural Therapy (CBT) + Video Feedback Therapy (VTF)	CBT + Progressive Muscle Relaxation (PMR)	Wellcome Trust grants (global charitable foundation) and Economic and Social Research Council. Target: public health action	Ext symptoms: CBCL	No significant treatment difference between the two groups. Outcome similar to the norms for non-clinical population
Verduyn et al. (2003) (UK)	*n* = 119 mother–child pairs Age: 2.6–4 y-o *M* = 37 months	Major depressive disorder or dysthymia	FGBI Cognitive Behavioural Therapy (CBT) group: mothers and children separately	Placebo group: community-based support or No treatment group: home visits for assessment	National Health Service Research and Development grant. Target: public health action	Ext symptoms: CBCL ECBI	No significant differences between the three groups. Post-hoc within-group analysis suggests significant improvement on CBCL in CBT group at post-test and follow-up ($t = 2.98$, df = 30, $p = 0.006$)
Substance use disorders							
Catalano et al. (1999); Haggerty et al. (2008) (USA)	*n* = 144 parents *n* = 178 children Age: 3–14 y-o *M* = 8.21 y-o	Substance use disorder Heroin addiction	FGBI Focus on Families project (FOF) + TAU	Methadone TAU	NIDA (federal agency) and Therapeutic Health Services (nationally accredited non-profit agency). Target: public health action	Incidence of substance use disorder: CIDI	Significant reduction in risk of developing a SUD in intervention group male compared to control group male (HR 0.53, $p = 0.03$) at long-term follow-up

Kelley & Fals-Stewart (2002) (USA)	*n* = 64 couples to drug treatment *n* = 71 couples to alcohol treatment Age: 6–16 y-o *M* = 9.3/10.7 y-o	Men with abuse or dependence for a psychoactive substance use disorder	PBI Behavioural Couple Therapy (BCT) for couple or Individual-Based Treatment (IBT): men only	Psychoeducational attention control treatment (PACT): 20 individual sessions + 12 lecture couple sessions	NIDA Grant + Alpha Foundation. Target: public health action	Ext symptoms: PSC	Significant improvement of PSC score in BCT group (*M* = 14.0, s.d. = 13.6) compared to IBT and PACT, for both drug and alcohol abuse, at post-test and 12-month follow-up
Lam et al. (2008) (USA)	*n* = 30 parent–child pairs Age: 8–12 y-o *M* = 8.9 y-o	Fathers with alcohol abuse or dependence	PBI Parents Skills with Behavioural Couples Therapy (PSBCT) group or Behavioural Couples Therapy (BCT) group	Individual-Based Treatment (IBT): only men, 12 individual sessions + 12 standard care	NIAAA Grant. Target: public health action	Depressive symptoms: CDI Anxiety symptoms: RCMAS Int/ext symptoms: CBCL	Significant improvement on all measures at post-test, 6 and 12-month follow-up in PSBCT ($p < 0.05$). Medium effect size (*r*s range from 0.25 to 0.46) between PSBCT and IBT on CDI and RCMAS across 12-month follow-up
Stanger et al. (2011) (USA, China)	*n* = 47 mother–child pairs Age: 2–7 y-o *M* = 3.7 y-o	Mothers with substance abuse or dependence	PBI Parent Training + Incentives (PTI): compensation for treatment compliance	Parent Training (PT): without incentives	NIDA and NIAAA grants. Target: public health action (community)	Int/ext symptoms: CBCL	Significant lower externalizing scores in PTI group at post-test (ITT). Significant effects on both internalizing and externalizing scores in PTI group among complier mothers with a dose response (CACE analyse)
Zhang et al. (2018) (USA)	*n* = 183 mothers Age: 8–16 y-o *M* = 11.5 y-o	Substance use disorder	FBI Ecologically-Based Family Therapy (EBFT)-Home or EFBT-Office + TAU	Women's Health Education (WHE): mothers only, 12 sessions + TAU	NIDA grant. Target: public health action	Int/ext symptoms: CBCL explored in sub-groups: declining, stable or increasing (substance use and psychological control) group	No estimation performed of CBCL scores differences in the EBFT and WHE groups. Significant lower level of int/ext symptoms in declining and stable groups. Significant lower int. symptoms in stable group
Anxiety disorders							
Ginsburg (2009); Ginsburg et al. (2015, 2020); Pella et al. (2017) (USA)	*n* = 136 families Age: 6–13 y-o *M* = 8.7 y-o	Current anxiety disorder	FBI Coping and Promoting Strength intervention (CAPS)	Information-Monitoring Condition: 36-pages pamphlet	NIMH Grant. Target: public health action (community)	Incidence of child anxiety disorder: The Anxiety Disorders Interview Schedule	Significant lower incidence of anxiety disorder in the CAPS (5.26% *v.* 30.65%, OR = 8.54, NNT = 3.9). Rate of onset: 6.6 times

(*Continued*)

Table 2. (*Continued.*)

Study	Participants/ age	Parental disorder	Intervention	Control	Funding and target audiences	Outcomes	Main results and interpretation
						Int/ext symptoms: CBCL SCARED	higher in the control group during the 1-year period (HR = 6.6, p = 0.002). Significant lower anxiety symptoms and behaviour problems at post-test, 6 and 12-month follow-up in the CAPS. 6-year follow-up: no group differences in the cumulative incidence of anxiety disorders
Mixed disorders							
Van Santvoort et al. (2014) (The Netherlands)	n = 254 families Age: 8–12 y-o M = 10.2	Any mental disorder or substance use disorder	YGBI Support group for children: youth group + 1 meeting for parents and 1 family final talk	Waiting list: 3 group-based leisure activities. Support group after 6 months	ZonMw grants (the Dutch Organization for Health Research and Development). Target: public health action	Int/ext symptoms: SDQ	No significant differences between groups. Significant improvement on SDQ in both groups

BASC, Behaviour Assessment System for Children; BSI, Behavioural Symptoms Index; BSQ, Behavioural Screening Questionnaire; CBCL, Child Behaviour Check List (-SS: syndrome scales; -BS: broadband scales); CBQ, Child Behaviour Questionnaire; CDI, Children's Depression Inventory; CDRS-R, Children's Depression Rating Scale Revised; CES-D, Center for Epidemiologic Studies Depression scale; CIDI, Composite International Diagnostic Interview; C-TRF, Caregiver-Teacher Report; DSR, Depression Symptom Rating; ECBI, Eyberg Child Behaviour Inventory; FBI, Family-Based Intervention; FGBI, Family Group-Based Intervention; HAM-D, Hamilton Depression Rating Scale; Int/ext, internalizing/externalizing symptoms; K-SADS, Kiddie Schedule for Affective Disorders and Schizophrenia (-E: Epidemiological, -PL: Present and Lifetime Version); M, mean age; MBI, Mother-Based Intervention; MDD, major depressive disorder; NIAAA, National Institute on Alcohol Abuse and Alcoholism; NIDA, National Institute on Drug Abuse; NIMH, National Institute of Mental Health; PBCL, Problem Behaviour Check List; PBI, Parent-Based Intervention; PSC, Pediatric Symptom Checklist; RCMAS, The Revised Children's Manifest Anxiety Scale; SCARED, Screen for Child Anxiety Related Disorders; SDQ, Strengths and Difficulties Questionnaire; TAU, treatment as usual; YGBI, Youth Group-Based Intervention; YSR, Youth Self-Report.

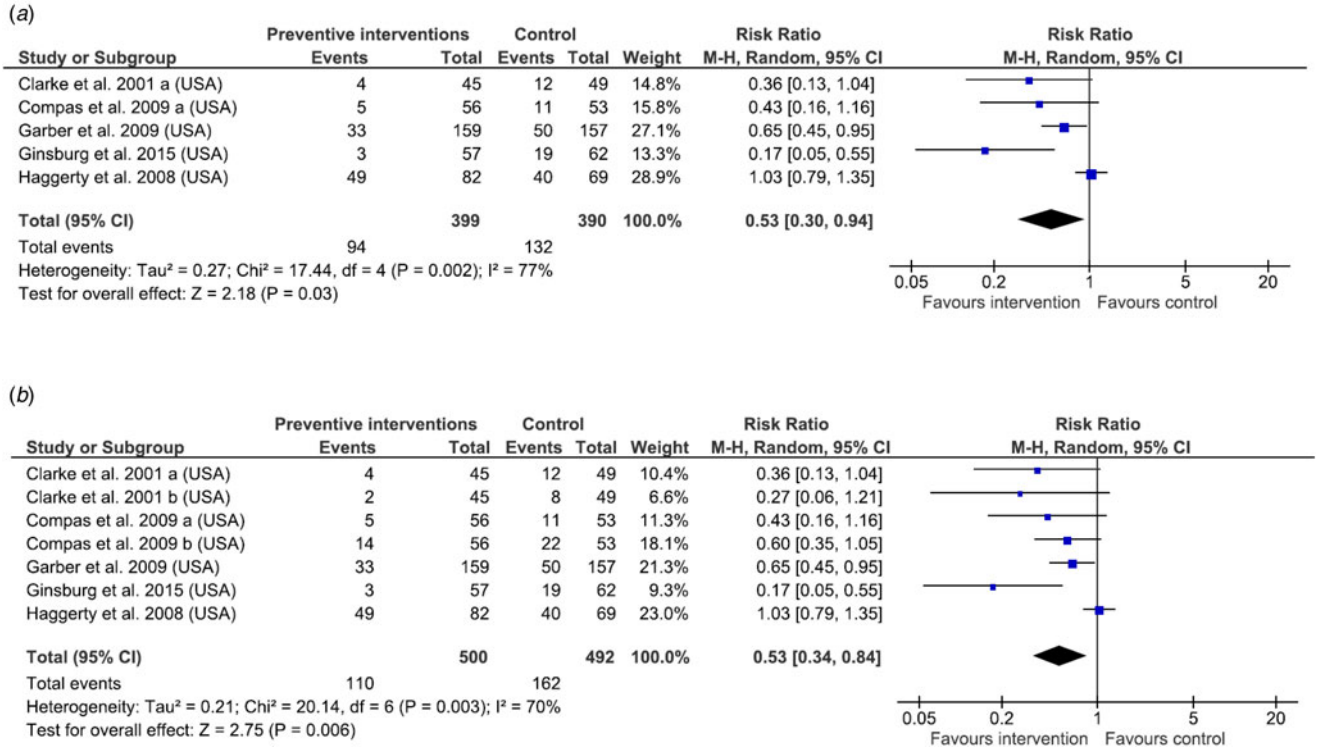

Fig. 2. Forest-plots of the effect of intervention *v.* any control condition on the risk in children to develop mental disorders. Note: (*a*) Incidence of the same mental disorders in children; (*b*) incidence of any mental disorders in children.

on positive, child-centred methods of control, to focus on cognitive management of mood and to support interactions with reinforcement of positive family relationships.

Psychoeducation

Psychoeducational techniques were evaluated in nine trials (Catalano, Gainey, Fleming, Haggerty, & Johnson, 1999; Giannakopoulos, Solantaus, Tzavara, & Kolaitis, 2021; Jones et al., 2017; Kelley & Fals-Stewart, 2002; Lam, Fals-Stewart, & Kelley, 2008; Pella, Drake, Tein, & Ginsburg, 2017; Solantaus, Paavonen, Toikka, & Punamäki, 2010; Stein et al., 2018; Van Santvoort et al., 2014), sometimes associated with CBT approaches. Interventions targeted parents with mood disorders, substance use disorders (in association with behavioural couple therapy) or anxiety disorders. They could take place at the clinic (with group sessions) or at home (home visits or online self-management).

The aim of family approaches was to target theory-driven modifiable child and parent risk factors, with an improvement of the communication and a deeper understanding of mental illness and its impact on family members. Families were taught how to identify the signs of the parents' disorder and how to reduce them. Parenting skills training focused on the improvement of communication, positive behavioural exchanges and problem-solving skills.

Other approaches

One trial (Murray et al., 2003) assessed a psychodynamic approach for mothers suffering from post-partum depressive symptoms, aiming at understanding mothers' representations of their infant by exploring the aspects of their own early attachment history.

In two studies (Forman et al., 2007; Lenze, Potts, Rodgers, & Luby, 2020), an interpersonal therapy for these mothers was evaluated, respectively based on a biopsychosocial perspective (targeting interpersonal problems, including interpersonal conflicts, social role transitions and loss and grief) and on attachment theory to explore the development of the mother–child dyadic relationship.

Other researchers (Coiro et al., 2012) reported, in parallel with a CBT group, a medication group for depressive mothers, consisting of taking an antidepressant treatment for 6 months.

A study evaluated a family system therapy (Zhang et al., 2018), focusing on mothers with a substance use disorder to target dysfunctional family interactions and identify factors contributing to maintain maternal symptoms. The efficacy of incentives (monetary prices) on compliance of parents with substance use disorders was also reported in another trial (Stanger, Ryan, Fu, & Budney, 2011).

Effects on children's outcomes

Incidence of mental disorders (five trials)

Forest-plots of the effect of intervention (*v.* any of the control conditions) on the incidence of mental disorders in children at post-intervention (same as parental ones or any disorders) are provided in Fig. 2.

The risk in the offspring of developing the same mental illness as the parent was decreased by 47% (Fig. 2*a*: combined RR = 0.53, range 0.17–1.03, 95% CI 0.30–0.94, $Z = 2.18$, $p = 0.03$). Results were similar for the risk of developing any mental disorder (Fig. 2*b*: combined RR = 0.53, range 0.17–1.03, 95% CI 0.34–0.84, $Z = 2.75$, $p = 0.006$).

There was statistical evidence of considerable and substantial between-trial heterogeneity (Fig. 2*a*: $I^2 = 77\%$, $p = 0.002$; Fig. 2*b*: $I^2 = 70\%$, $p = 0.003$, respectively). A sensitivity analysis identified an outlier (Haggerty, Skinner, Fleming, Gainey, & Catalano,

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2008) because of its very long-term follow-up (144 months compared to other studies with data from 6 and 12-month follow-up). Excluding this trial lowered heterogeneity to low levels ($I^2 = 47\%$, $p = 0.13$ and $I^2 = 25\%$, $p = 0.25$, respectively), but had no significant impact on the results.

Internalizing symptoms (12 trials)

The effect of the active interventions (*v.* any of the control intervention) on internalizing symptoms in children is provided in Fig. 3*a* at post-intervention (*A*: 0–4 months), short-term (*B*: 5–12 months) and long-term follow-up (*C*: 15–68 months).

One study (Coiro et al., 2012) included two separate comparison groups: CBT group (*a* in Fig. 3*a*) and medication group (*b* in Fig. 3*a*). Another study (Giannakopoulos et al., 2021) reported two measures of internalizing symptoms (*a*, anxiety symptoms and *b*, depressive symptoms in Fig. 3*a*).

Post-intervention effects were small but significant (SMD = −0.25, range −0.53 to 0.29, 95% CI −0.37 to −0.14, $Z = 4.43$, $p < 0.00001$, $I^2 = 0\%$), as well as short-term follow-up effects (SMD = −0.20, range −1 to 0.34, 95% CI −0.37 to −0.03, $Z = 2.33$, $p = 0.02$). Only five studies reported data at the long-term follow-up, and no effect of the intervention was found (SMD = 0.20, range −0.26 to 1.79, 95% CI −0.25 to 0.65, $Z = 0.88$, $p = 0.38$). Heterogeneity was significant but moderate at short-term ($I^2 = 46\%$, $p = 0.04$) and high at long-term follow-up ($I^2 = 87\%$, $p < 0.00001$). A sensitivity analysis identified an outlier (Van Doesum, Riksen-Walraven, Hosman, & Hoefnagels, 2008) which reported data at very long-term follow-up (68 months). Excluding this trial from the long-term follow-up group lowered the heterogeneity to non-significant low levels ($I^2 = 0\%$, $p = 0.42$), with no significant impact on the results. Subgroup analyses, including the type of intervention, the type of control groups, the presence or absence of children's and parents' symptoms at baseline and the age of children, failed to show significant subgroup differences (online Supplementary Fig. S1).

Externalizing symptoms (14 trials)

Figure 3*b* reports the effect of intervention on externalizing symptoms in children at post-intervention (*A*), short-term (*B*) and long-term follow-up (C).

One study (Kelley & Fals-Stewart, 2002) included two separate comparison groups: alcohol-abusing fathers (*a* in Fig. 3*b*) and drug-abusing fathers (*b* in Fig. 3*b*).

No significant effect of intervention was reported at post-intervention (SMD = −0.11, range −0.68 to 0.36, 95% CI −0.27 to 0.04, $Z = 1.42$, $p = 0.16$, $I^2 = 25\%$), short-term (SMD = 0.06, range −0.69 to 0.86, 95% CI −0.15 to 0.26, $Z = 0.56$, $p = 0.57$, $I^2 = 58\%$) and long-term follow-up (SMD = −0.04, range −0.20 to 0.30, 95% CI −0.22 to 0.14, $Z = 0.46$, $p = 0.65$, $I^2 = 30\%$). The sensitivity analysis identified no outliers. A subgroup analysis according to the presence or absence of children's symptoms at baseline revealed statistically significant subgroup differences [online Supplementary Fig. S2 (C), $\chi^2 = 7.45$, $p = 0.006$, $I^2 = 86.6\%$] and reduced heterogeneity to low levels for the no symptoms subgroup ($I^2 = 0\%$, $p = 0.84$) with a significant effect ($Z = 2.75$, $p = 0.006$). The other subgroup analyses founded non-significant differences (online Supplementary Fig. S2).

Publication bias

Online Supplementary Fig. S3 provided the funnel-plots of standard error (S.E.) against SMD for internalizing symptoms (A) and externalizing symptoms (B) at post-intervention. It seems that the studies were symmetrically distributed around the mean effect size, and Egger's tests suggested no evidence of publication bias ($p = 0.541$ and $p = 0.264$, respectively).

Discussion

This systematic review and meta-analysis identified 31 publications from 20 independent randomized controlled trials focused on preventive intervention in infants, children and adolescents of mentally ill parents. Most of the interventions were based on CBT approaches and psycho-educational techniques, either at home or in an outpatient clinic. The results of the meta-analysis showed that these interventions were efficacious on the risk of developing mental disorders in children, with a 47% reduction in risk. In addition, preventive interventions (compared to any control group) had a significant positive effect on internalizing symptoms after the intervention, during the first year.

Our results are in line with those of a previous study (Siegenthaler et al., 2012), and we found larger effects (with a greater reduction in the incidence of mental disorders in children).

To our knowledge, this is the first meta-analysis to explore the incidence of any mental disorders in offspring, and to assess both internalizing and externalizing outcomes at different follow-up periods (post-intervention, short-term and long-term) in this population. Only two trials (Clarke et al., 2001; Compas et al., 2015) assessed the incidence of mental disorders different from the parental ones, with no significant effect. Previous meta-analyses only explored the incidence of the same mental illness as parents in offspring (Loechner et al., 2018; Siegenthaler et al., 2012). However, the risk for children developing a mental disorder themselves is not a uniform and one-way process. A recent systematic review (Van Santvoort et al., 2015) examined the relationship between parental affective or anxiety disorders and children's diagnostic outcomes in 76 studies. The authors found that children of parents with affective disorders had more transgenerational multifinality (children with the same parental diagnostic were at risk of a broad spectrum of symptoms) and equifinality (children of parents with different diagnoses were at risk of the same problems) patterns, in line with the results of another study (Weissman et al., 2006). In contrast, when parents were affected by anxiety disorders, transgenerational specificity and concordance patterns were more prevalent, which means their children were mainly at risk to have the same disorder, with specifically related symptoms. Therefore, complex factors seem to be involved in the transmission of mental disorders, and children are at risk of developing various disorders and not only the same as their parents. In view of these results, investigation of the incidence of various diagnoses in offspring in future studies appears essential to explore broader effects of preventive interventions in this high-risk population.

Five studies (Brent et al., 2015; Compas et al., 2015; Garber et al., 2009; Pella et al., 2017; Stein et al., 2018; Van Santvoort et al., 2014) included booster sessions, between 3 and 10 months later, in addition to the acute treatment, with the aim of prolonging the effects. Among these studies, an overall effect was maintained at 12-month follow-up in one trial (Pella et al., 2017) and at 24-month follow-up in another trial (Compas et al., 2015). At 6-year follow-up, the maintenance of initial gains was true only in parents who were not depressed at baseline (Brent et al., 2015; Garber et al., 2009). The impact of additional

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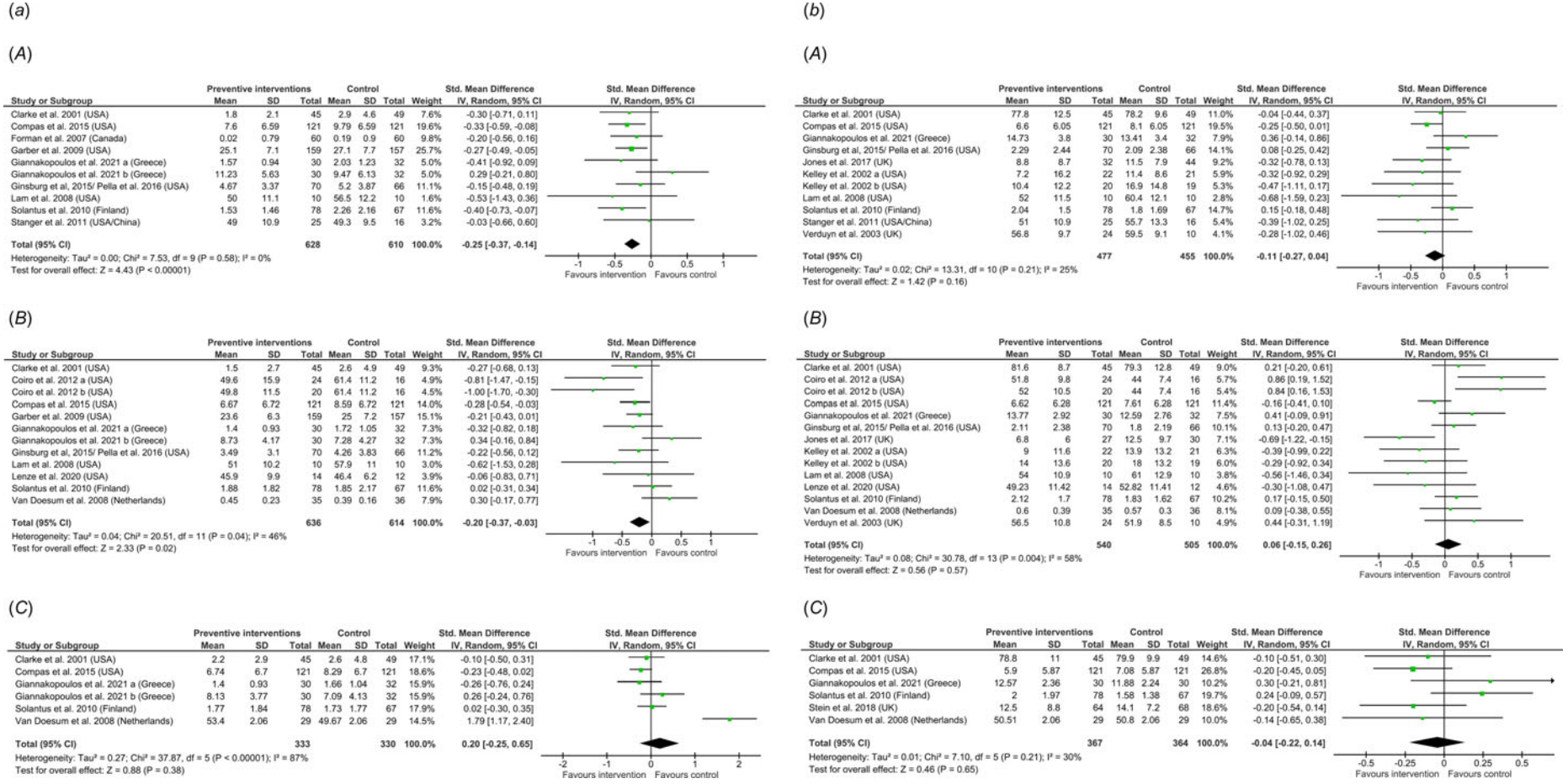

Fig. 3. Forest-plots of the effect of intervention *v.* any control condition in internalizing symptoms (*a*) and externalizing symptoms (*b*) in children over time. (*A*) At post-intervention follow-up; (*B*) at short-term follow-up; (*C*) at long-term follow-up.

reminder sessions over time therefore appears to be an interesting approach to sustain the effects of these interventions over the long term, but it needs to be studied more precisely and systematically in future research.

Our study is the first to evaluate the impact of several variables on the effect of preventive interventions in children of parents with mental illness. In their meta-analysis, Siegenthaler et al. (2012) failed to find evidence for an effect of children's participation in the interventions (*v.* interventions focused on parents only). In the present study, we performed five subgroup analyses: the recipients of the interventions (family including the child and at least one of the two parents, parents only, *v.* children only); the presence of symptoms in parents and their children at baseline; the age of children; and the use of active *v.* non-active control groups. A significant difference was found only for the subgroup of children with no symptoms at baseline, in externalizing outcomes, suggesting that children with few or no symptoms prior to the intervention may benefit more from an intervention. However, these results need to be interpreted with caution and have not been found for the internalizing symptoms. We can also note that the majority of the children included were between 3 and 12 years old, with only two studies focusing specifically on adolescents (Clarke et al., 2001; Garber et al., 2009). We did not find significant differences in our subgroup analyses and it would be interesting in future research to study the impact of interventions on different age groups in order to compare their effectiveness according to the developmental stage of the children.

Another interesting consideration is the high level of variability in the attrition rates of participation in intervention, which requires a better identification of the factors that improve compliance in participants. For example, only 39% of women completed a substantial number of sessions in a CBT group intervention with distinct sessions for mothers and children in an outpatient clinic (Verduyn et al., 2003), while 90.3% of mothers attended at least nine out of 13 sessions when the intervention was delivered at home (Stein et al., 2018). The drop-out rate was also highly variable and important, especially in long-term follow-ups, often reported as a limitation in the included studies. We found that five studies used monetary compensation to enhance participation and assessment completion, in particular with low-income parents suffering from substance use disorders (online Supplementary Table S2). Among them, one trial examined the effect of monetary incentives in addition to a parent training intervention for parents with substance use disorders (Stanger et al., 2011). Surprisingly, homework completion and session attendance did not differ between the experimental and the control group, but higher rates of daily monitoring were highlighted in the group with incentives (twice as often as control group). The authors found an improvement of behavioural symptoms in the experimental group, suggesting that this daily intervention, improved by the incentives and combined with weekly groups, contributed significantly to the better outcomes observed in the experimental group. This might suggest that the improvement of family's engagement and retention is essential to implement preventive interventions in the most effective way. An earlier review of 17 randomized controlled trials (Ingoldsby, 2010) of interventions to enhance family participation in parent and child mental health programs reported four types of interventions improving family engagement: brief early treatment engagement discussions, family systems approach, interventions focusing on enhancing coping and family support, and motivational interviewing. Engaging families with a severe mental illness in an intensive program can be complicated. Interventions can be experienced as intrusive for families, and communication about the risk of parental mental illness for offspring can be perceived as stigmatizing and guilt-ridden for the parents. Participation and retention of families are critical issues for clinical practices, and those dimensions must be taken into account in the evaluation of the effectiveness of preventive interventions.

This brings up the question of the generalizability of these results in clinical practice. Some studies focused on a very selective sample (Brent et al., 2015; Clarke et al., 2001) and were difficult to transpose to a real-life setting. Moreover, participants' differences between studies, particularly in regard to the severity of mental illness, comorbidities and socio-economic background, do not allow to generalize the results to a larger and different clinical population. Targeting parents with severe mental illness who did not seek help led to engagement difficulties in the recruitment process (difficulties in making contact, refusal to participate in the intervention, etc.). Other enrolment strategies, close to the patients' living environment, could be more interesting (for instance through general practitioners, schools or Internet). Another study (Stuart, Bradshaw, & Leaf, 2015) provided an overview of existing designs and analysis methods for enhancing external validity of randomized controlled trials to target populations, and their limitations. Further studies are required to extend these results to population encountered in real-life clinical practice. For instance, future studies could include qualitative analyses, to collect parents' experience of intervention and assess their acceptability. Moreover, most of the trials were conducted by the team who developed the intervention. Replication studies are needed, including in other settings (less selective population, more naturalistic conditions, etc.). Finally, both the lack of geographical diversity of the included trials (the vast majority of clinical trials were conducted in the USA and for substance use disorders in particular, all studies were conducted in the USA), and of racial and ethnic diversity in the included samples, limited the generalizability of our results to all racial and ethnic groups (Sue, Zane, Nagayama Hall, & Berger, 2009) and to all health care systems.

Our study was limited by the relatively low number of trials included on the final screening and their small samples (only three studies included more than 200 participants). However, our study's strict inclusion criteria allowed for the inclusion of rigorously selected trials as well as more homogeneous samples, than in previous meta-analyses (Siegenthaler et al., 2012; Thanhäuser et al., 2017). Moreover, our search found no trials on parents with a psychotic disorder, and future trials in this specific population are warranted.

Another limitation is that most studies used only one informant's report for symptoms scales, especially parental reports, while it has been reported that parents with depression or substance use disorder might be less sensitive indicators of intervention effects (Compas et al., 2015; Lam et al., 2008; Zhang et al., 2018). Future trials should assess outcomes using multiple informants, including parents, children, as well as others such as teachers, to prevent this bias.

In conclusion, this meta-analysis should be regarded as a step towards the implementation in clinical practice of preventive interventions for children and adolescents of parents with a mental illness. Through the analysis of 17 trials, we found evidence of positive effects of preventive interventions in the offspring of mentally ill parents, with a decrease of the risk of onset of mental disorders in children and of internalizing symptoms. Future studies should include an evaluation of the acceptability of these interventions and a study of potential moderating factors, in order to

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improve the therapeutic alliance and thus the clinical impact on this high-risk population.

Supplementary material. The supplementary material for this article can be found at https://doi.org/10.1017/S0033291721003366.

Author contributions.
AL and AR designed the study and wrote the protocol. AL and AR independently conducted the systematic review and AL produced the first draft of the manuscript. AR oversaw all aspects of the research. AR and EB drafted portions and substantively edited all drafts of the manuscript. AL, AR and EB analysed the data. CA and JPR critically revised the manuscript for important intellectual content. All authors contributed to and have approved the final manuscript. AL, AR and EB take responsibility for the integrity and the accuracy of the data analysis.

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Conflict of interest. None.

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