# Psychosocial and psychological interventions for relapse prevention in schizophrenia: a systematic review and network meta-analysis

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## Summary

**Background** Many psychosocial and psychological interventions are used in patients with schizophrenia, but their comparative efficacy in the prevention of relapse is not known. We aimed to evaluate the efficacy, acceptability, and tolerability of psychosocial and psychological interventions for relapse prevention in schizophrenia.

**Methods** To conduct this systematic review and network meta-analysis we searched for published and unpublished randomised controlled trials that investigated psychosocial or psychological interventions aimed at preventing relapse in patients with schizophrenia. We searched EMBASE, MEDLINE, PsycINFO, BIOSIS, Cochrane Library, WHO International Clinical Trials Registry Platform, and ClinicalTrials.gov up to Jan 20, 2020, and searched PubMed up to April 14, 2020. We included open and masked studies done in adults with schizophrenia or related disorders. We excluded studies in which all patients were acutely ill, had a concomitant medical or psychiatric disorder, or were prodromal or "at risk of psychosis''. Study selection and data extraction were done by two reviewers independently based on published and unpublished reports, and by contacting study authors. Data were extracted about efficacy, tolerability, and acceptability of the interventions; potential effect moderators; and study quality and characteristics. The primary outcome was relapse measured with operationalised criteria or psychiatric hospital admissions. We did random-effects network meta-analysis to calculate odds ratios (ORs) or standardised mean differences (SMDs) with 95% CIs. The study protocol was registered with PROSPERO, CRD42019147884.

**Findings** We identified 27 765 studies through the database search and 330 through references of previous reviews and studies. We screened 28 000 records after duplicates were removed. 24 406 records were excluded by title and abstract screening and 3594 full-text articles were assessed for eligibility. 3350 articles were then excluded for a variety of reasons, and 244 full-text articles corresponding to 85 studies were included in the qualitative synthesis. Of these, 72 studies with 10 364 participants (3939 females and 5716 males with sex indicated) were included in the network meta-analysis. The randomised controlled trials included compared 20 psychological interventions given mainly as add-on to antipsychotics. Ethnicity data were not available. Family interventions (OR 0·35, 95% CI 0·24–0·52), relapse prevention programmes (OR 0·33, 0·14–0·79), cognitive behavioural therapy (OR 0·45, 0·27–0·75), family psychoeducation (OR 0·56, 0·39–0·82), integrated interventions (OR 0·62, 0·44–0·87), and patient psychoeducation (OR 0·63, 0·42–0·94) reduced relapse more than treatment as usual at 1 year. The confidence in the estimates ranged from moderate to very low. We found no indication of publication bias.

**Interpretation** We found robust benefits in reducing the risk of relapse for family interventions, family psychoeducation, and cognitive behavioral therapy. These treatments should be the first psychosocial interventions to be considered in the long-term treatment for patients with schizophrenia.

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## Introduction

Schizophrenia is one of the most debilitating disorders worldwide.[1] Relapse is associated with high costs for hospital admissions and unemployment and loss of productivity. Additionally, relationships are often jeopardised and there is a risk of suicide.[2] This situation has an impact in terms of burden for patients, families and society.

Antipsychotics are effective for the prevention of relapse,[3] but they are associated with considerable side-effects, and according to a Cochrane review, 24% of patients relapse within 1 year despite drug treatment.[4,5] Various psychosocial and psychological interventions have been developed for people with schizophrenia. Such non-pharmacological interventions might play an important role in the prevention of psychotic episodes.[6–9]

However, several major limitations to the available body of evidence regarding psychosocial interventions in the maintenance therapy of schizophrenia have been identified. Firstly, previous reviews were not specifically

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## Research in context

### Evidence before this study

Schizophrenia is a common, severe, and usually chronic disorder. Psychosocial and psychological interventions can be used in combination with antipsychotics for preventing recurrence of psychotic episodes (relapse) in patients with schizophrenia. However, many different interventions have been developed, and whether they differ in terms of efficacy for relapse prevention, and to what extent, remains unclear. We searched PubMed (last search April 27, 2021), without language restrictions, with the search term (((schizophrenia)) AND (psychotherapy OR "psychological intervention" OR "psychological treatment" OR "psychosocial intervention" OR "psychosocial treatment")) AND ((maintenance OR relapse)) and filter "Article type: Meta-analysis", and with the search term ((((schizophrenia)) AND (psychotherapy OR "psychological intervention" OR "psychological treatment" OR "psychosocial intervention" OR "psychosocial treatment")) AND ((maintenance OR relapse)) ) AND (network meta-analysis) and inspected 65 references. We found no network meta-analyses, and some outdated pairwise meta-analyses investigating single interventions compared with treatment as usual, except for two Cochrane reviews that compared cognitive behavioural therapy and brief psychoeducation with other psychosocial interventions as a group. Excluding these Cochrane reviews, we found no evidence on the comparative effectiveness of psychological and psychosocial interventions for the prevention of relapse in schizophrenia. Moreover, these meta-analyses did not specifically focus on relapse prevention, but rather investigated each intervention on multiple outcomes in the general population of patients with schizophrenia, including patients who were acutely ill.

### Added value of this study

This study provides an overall picture of all the available evidence on comparative efficacy, acceptability, and tolerability of psychosocial and psychological interventions for relapse prevention in people with schizophrenia. We found a clear benefit in reducing the risk of relapse for family interventions, family psychoeducation, and cognitive behavioural therapy.

### Implications of all the available evidence

We suggest that policy makers and clinicians consider giving priority to family interventions, family psychoeducation, and cognitive behavioural therapy when allocating resources and planning maintenance treatment for patients with chronic schizophrenia.

focused on the maintenance treatment of stable patients, but rather on the general population of patients with schizophrenia, mainly in the acute phase, and just measured relapse among many other outcomes.[6–9] Secondly, the evidence is limited to pairwise meta-analyses that investigated single interventions, mainly in comparison with standard care, and only two Cochrane reviews have compared psychological interventions for the prevention of relapse directly with each other.[10,11] With these two exceptions, psychological interventions for the prevention of relapse have not been compared with each other, resulting in no information on a comprehensive ranking of all psychosocial interventions evaluated in randomised controlled trials for the prevention of relapse in patients with schizophrenia. Finally, the length of time that these interventions should be provided for remains unclear, because in previous reviews, the results at different time points were not always consistent.[6–9]

A better understanding of the comparative efficacy of these active interventions would be important for clinical practice and for meaningful allocation of resources. In this context, we did a network meta-analysis to calculate relative treatment effects of psychosocial interventions for relapse prevention in patients with schizophrenia in terms of the following: (1) relapse, considering three different time-points, up to 26 weeks, up to 52 weeks, and beyond; (2) other efficacy outcomes; and (3) acceptability (number of dropouts) and tolerability (adverse events).

## Methods

### Search strategy and selection criteria

In our systematic review and network meta-analysis, we included open and masked randomised controlled trials done in adults with a diagnosis of schizophrenia or related disorders, irrespective of the diagnostic criteria, without restrictions of setting, gender, or ethnicity. Studies including participants with other diagnoses were included if at least 80% of the participants had a diagnosis of schizophrenia, schizophreniform, or schizoaffective disorder. We excluded studies in which the inclusion criteria was acute illness, a concomitant medical or psychiatric disorder, or prodromal or "at risk of psychosis", to ensure homogeneity in the population. Studies in which the psychosocial intervention started at the end of a period of time in hospital were included, because such a procedure is common practice.

We included studies that compared psychosocial and psychological interventions that had a main target of relapse prevention. The interventions could be compared with each other or with control conditions used in the trials, usually treatment as usual. In this control condition, participants receive the standard care, which usually includes maintenance treatment with antipsychotics, but no additional specific psychosocial intervention. We included studies irrespective of publication year and language.

Since our aim was to include studies in which the psychosocial intervention is intended to prevent relapse, studies were included if relapse or rehospitalisation were

measured among the primary outcomes according to the protocols or methods of the trial. For studies in which this information was not explicitly reported, two reviewers (IB and AR) independently judged whether relapse could be considered a primary or co-primary outcome of the treatment by assessing the title, outcomes structure, study aims, and power calculations. A detailed list of criteria used is reported in the appendix (p 18). We included studies in which the assessment of relapse was done at a minimum of 12 weeks after randomisation.

To identify eligible studies, we searched EMBASE, MEDLINE, PsycINFO, PubMed, BIOSIS, Cochrane Central Register of Controlled Trials, ClinicalTrials.gov and WHO International Clinical Trials Registry Platform for randomised controlled trials published up to Jan 20, 2020, and in PubMed up to April 14, 2020, that compared psychosocial interventions for relapse prevention with each other or with a control condition in people with schizophrenia. The search terms included terms related to schizophrenia and schizophrenia-like disorders, randomisation, and a great variety of terms related to psychosocial interventions (appendix pp 8–17).

IB and either AR or HG-M independently screened the identified references and selected the finally included studies. IB and AR extracted data from the selected studies, considering all available reports. Relevant information was entered into a Microsoft-Access database especially created for this study that automatically detected whether independent extractions agreed.

HW and DW managed the selection and data extraction of studies written in Chinese. Disagreements were resolved by discussion among reviewers or with a third reviewer (SL). Additionally, IB contacted authors of included studies published in the past 30 years with a request for missing or additional data (appendix pp 19–24).

### Data analysis

The primary outcome was relapse. In case of multiple measures reported, we gave priority to relapse defined with operationalised criteria, psychiatric hospital admissions, and clinical judgement, in this order. We extracted data for relapse at three different timepoints separately (up to 6 months, up to 12 months–primary time point, more than 12 months).

We examined overall, positive, negative, and depressive symptoms of schizophrenia; quality of life; adherence; overall functioning; and study discontinuations due to inefficacy as secondary efficacy outcomes. Study discontinuations for any reason were examined as a measure of acceptability. Adverse events that might have been connected to the intervention (reported according to a published classification)[12] and mortality (for any reason, due to natural causes or suicide) were examined as tolerability outcomes. Data for secondary outcomes were extracted at study endpoint (end of the treatment).

The psychological interventions were classified according to the description provided in each study publication, with a definition of nodes described in the table).

In case we retrieved more reports of the same study, data was extracted from the one reporting about the highest number of patients.

We performed random-effects pairwise meta-analyses and a network meta-analysis in a frequentist framework using the package netmeta in R (version 1.2-1).[13] We calculated odds ratios (ORs) for binary outcomes and standardised mean differences (SMDs) for continuous outcomes, both presented with 95% CIs. We also calculated the relative ranking for each intervention within the frequentist framework (as P-scores) and used them to present the results according to this order.[14] To facilitate interpretation of results, we calculated absolute event rates for the primary outcome relapse at the primary time-point 12 months (appendix p 3).

See Online for appendix

Before running the network meta-analysis, we assessed the transitivity assumption. This assumption implies that studies comparing different sets of interventions are sufficiently similar to provide valid indirect inferences, which we tried to ensure by applying narrow inclusion criteria. We also compared the distribution of key effect modifiers across studies grouped by interventions (baseline severity, inpatient status, masking of outcome assessor, percentage of female patients, publication year, sample size, mean age, study duration).

We assumed a common heterogeneity parameter across the various treatment comparisons and presented the between-study variance $\tau^2$ for each outcome. We characterised the amount of heterogeneity as low, moderate, or high using the first and third quantiles of their empirical distributions.[15,16]

To explore potential sources of heterogeneity or inconsistency, we did a priori planned subgroup analyses for the primary outcome on the following potential effect modifiers:[17] first-episode patients, setting (individual *vs* non-individual), inpatient status, number of sessions, and baseline severity.

Statistical inconsistency was evaluated separating indirect from direct evidence, and then testing the agreement of these two pieces of evidence (SIDE-test);[18] the magnitude of inconsistency factors (ratio of ORs) and their respective p values were used to identify the presence of inconsistency. We also applied the design-by-treatment interaction model that evaluates inconsistency in the network.[19]

Sensitivity analyses were done excluding studies that did not employ a masked outcome assessor, studies that presented only completer analyses, studies with high overall bias, studies with researchers' allegiance, or studies in which relapse or hospital admission were not defined explicitly as primary outcome (but only based on our judgement; appendix p 18). We also analysed hospital admissions and relapse separately. We did a sensitivity analysis considering patients who dropped out from the study as having relapsed (unless data about these patients

| | Number of studies | Description of the intervention |
|---|---|---|
| Acceptance and commitment therapy | 1 | A manualised third-generation behavioural therapy that incorporates acceptance and mindfulness-based strategies to help patients in overcoming negative thoughts and feelings. |
| Assertive community treatment | 3 | An intensive, highly integrated approach for community mental health service delivery. The teams visit the patients at home, provide clinical assessments and crisis interventions, along with psychosocial and functional assistance. This can be considered as a more active form of case management, because it is more holistic and integrated with coordinated services that promote increased wellness for the patient. |
| Case management | 3 | Each patient is usually assigned to a case manager who contacts the patient regularly (eg, once a week) and can provide more intensive support in case of particularly acute needs. |
| Cognitive behavioural therapy | 9 | Cognitive behavioural therapy for psychosis is usually based on an individualised case formulation and the establishment of collaborative goals with the patient. Therapy components include the improvement of existing coping strategies, the development and practice of new ones, the modification of delusional beliefs and beliefs about hallucinations, and the challenge of dysfunctional schemas. Adaptive views of self are strengthened, including the re-evaluation of negative beliefs about the self. |
| Cognitive training | 1 | A programme of regular activities aimed to maintain or improve cognitive abilities. In the specified study, the patients received training of memory and attention, training of language expression and logic, coordination, and cognitive rehabilitation. |
| Family interventions | 19 | An intervention involving the relatives of the patient, which can have several different aims. These include construction of an alliance with relatives who care for the person with schizophrenia, reduction of adverse family atmosphere, enhancement of the capacity of relatives to anticipate and solve problems, maintenance of reasonable expectations for patient performance, and attainment of desirable change in relatives' behaviour and belief systems. |
| Family psychoeducation | 15 | Similar to psychoeducation for patients, the following areas are usually covered: symptoms of schizophrenia, pharmacological and psychosocial treatments, and prevention of relapse, with a special focus on the role of the family. The intervention might be delivered to the relatives alone, involve the patient, or be delivered in a multi-family context. More active aspects such as coping skills might be involved, but the primary focus is the provision of information. |
| Family support | 2 | Mainly used as a control condition for family interventions; the aim is to control for the non-specific aspect of the treatment (for example, spending time with families that experience the same situation, without the provision of a systematic intervention (also defined as the social network placebo). |
| Health education | 2 | Lectures on general health topics (such as healthy food or physical exercise); might include relaxation training and stress reduction techniques. |
| Integrated interventions | 11 | Interventions that were explicitly defined as a combination of different treatments, for example individual cognitive behavioural therapy plus family intervention plus assertive outreach. |
| Mindfulness | 1 | The intervention consists of guided meditation followed by reflective group discussion aimed at facilitating understanding or metacognitive insight. During meditation, participants bring full awareness to difficult voices, feelings, thoughts, and images, and also become aware of habitual coping reactions, safety behaviours, and their effects. In meditation they practise letting go of these reactions and learn to allow and observe psychotic experiences without reacting. Meditation and discussion lead to insight that struggling, judging, and ruminating on psychotic experience creates distress, while mindful observation and acceptance of psychotic experience is empowering and calming. |
| Motivational interviewing | 2 | A client-centered, directive method, through which patients are engaged in strategically directed conversations about their problems. It explores personal ideas and ambivalences, eliciting and selectively reinforcing so-called change talk, by which discrepancies between the present behaviour and the patient's own future goals are amplified. The overall goal is to increase the patient's intrinsic motivation for change. In patients with schizophrenia it can be used to focus on specific impacts of illness behaviours on the patients, and provide them with opportunities to engage and discuss their ambivalent attitudes towards their illness behaviours, treatments, and possible consequences of non-adherence. |
| Psychoeducation (for patients) | 9 | Psychoeducation can be defined as the education of a person with a psychiatric disorder in subject areas that serve the goals of treatment and rehabilitation. In patients with schizophrenia it usually covers the following topics: symptoms of psychosis, models of psychosis, effects and side-effects of medication, maintenance medication, psychotherapy for psychosis, early symptoms of relapse, and relapse prevention. |
| Rehabilitation | 6 | Usually includes a prevocational day programme, recreational and social activities, apartment living, and transitional employment opportunities with the aim of increasing the ability of the patient to function independently in the community. |
| Relapse prevention programmes | 2 | Interventions that generally include education for recognising early symptoms of relapse, a system of symptoms monitoring, and a crisis plan and intervention in case the symptoms increase over a certain threshold. |
| Relatives groups | 5 | Support groups for relatives of patients, where they meet without the patients with the aim of sharing experiences and providing mutual support and emphatic discussion about caregiving experiences. The groups are usually peer led, without the direct involvement of an expert. The peer leader facilitates empathic and supportive responses to individual needs and concerns. |
| Social skills training | 5 | An intervention for acquiring skills necessary to live in the community. It includes teaching skills such as symptom management and relapse prevention, involving role-plays, problem solving, in vivo exercises, and home assignments. The therapists are instructed to model appropriate interaction styles and behaviours, and to teach clients how to effectively use the skills by using repetition and encouragement. |
| Supportive therapy | 3 | A group active intervention, aimed at the provision of a safe and supportive atmosphere in which to raise issues of emotional importance to the patients, with an emphasis on the non-specific factors of warmth and empathy. Patients can describe the narrative of their lives, including the effect of the illness, so that they can be helped to make sense of the timing of the illness and its nature and content with reference to strong and unbearable effects regarding past aspects of personal history. |
| Telemedicine | 4 | Patients and family members are regularly contacted via SMS or telephone call with the main aim of monitoring symptoms. If the symptoms appear to be above a certain threshold, an alert is activated and a visit with the clinician is organised. |
| Treatment as usual | 61 | Patients continue to receive standard psychiatric care. This can vary according to national and local service protocols and guidelines, but usually includes regular psychiatric consultations, maintenance antipsychotic medication, out-patient and community follow-up, and access to community-based rehabilitative activities such as day centres and drop-in centres. |

***Table:*** **Description of included interventions**

were already considered by study authors in the outcome provided in the study; for these studies we did not do this additional analysis to avoid double counting). In the main analysis, patients who dropped out from the study were not considered as having relapsed, unless explicitly stated.

Risk of bias was assessed by IB and AR using the Cochrane Risk of Bias tool 2 for the primary outcome relapse.[20] The tool evaluates the domains randomisation process, deviations from intended interventions, missing outcome data, measurement of the outcome, and selection of the reported result. We assessed the presence of small-trial effects (potentially associated with publication bias) for the primary outcome with a comparison-adjusted funnel plot ordering the treatments from the newest to the oldest. Following this, we tested for asymmetry in the adjusted logORs using the Harbord-test.[21,22]

We evaluated the confidence in the relative treatment effect estimated in the network meta-analysis for the primary outcome using the Confidence in Network Meta-Analysis framework,[23] implemented in the web application CINeMA.[24]

We followed the PRISMA statement extension for network meta-analyses (appendix pp 5–7).[25] The methods of the systematic review and network meta-analysis are described in detail in the protocol registered in PROSPERO, CRD42019147884; in the appendix (p 3); and in a specific method paper.[17]

### Role of the funding source

The funder of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

## Results

27765 studies were identified through the database search and 330 identified through references of previous reviews and studies. 28000 records were screened after duplicates were removed. After 24406 records were excluded during title and abstract screening, 3594 full-text articles were assessed for eligibility. Following exclusion of a further 3350 articles for a variety of reasons including different study design, inappropriate population, and incorrect intervention, 244 full-text articles corresponding to 85 studies were included in the qualitative synthesis. Of these, 72 studies (involving 10364 participants and done between 1971 and 2019) had usable data and were included in the network meta-analysis; figure 1; appendix pp 25–35).

We were able to include unpublished data for nine studies, owing to collaboration with the authors (appendix pp 19–24). The included studies provided comparisons of 20 psychosocial and psychological interventions (table).

The mean sample size per study was 142 participants (range 19–1268), and the median trial duration was 52 weeks (range 2–468). Of 9655 participants with sex indicated, 3939 (40·8%) were female and 5716 (59·2%) were male. We tried to collect ethnicity data, but they were rarely reported. The mean duration of illness was 7·6 years (SD 4·2), and the mean age of participants was 32·3 years (SD 6). Most patients had mild symptoms of schizophrenia, with a mean reported Positive and Negative Syndrome Scale baseline score of 52·34.[26]

The risk of bias assessments for the included studies are presented in the appendix (pp 36–39). One study had a low overall risk of bias, 51 studies had a moderate overall risk, and 33 studies had a high overall risk. No study was rated at high risk in the randomisation process domain.

We found no clear evidence of violations of the transitivity assumption when comparing characteristics of studies across interventions (appendix pp 40–48). However, in most parameters the number of studies per comparison

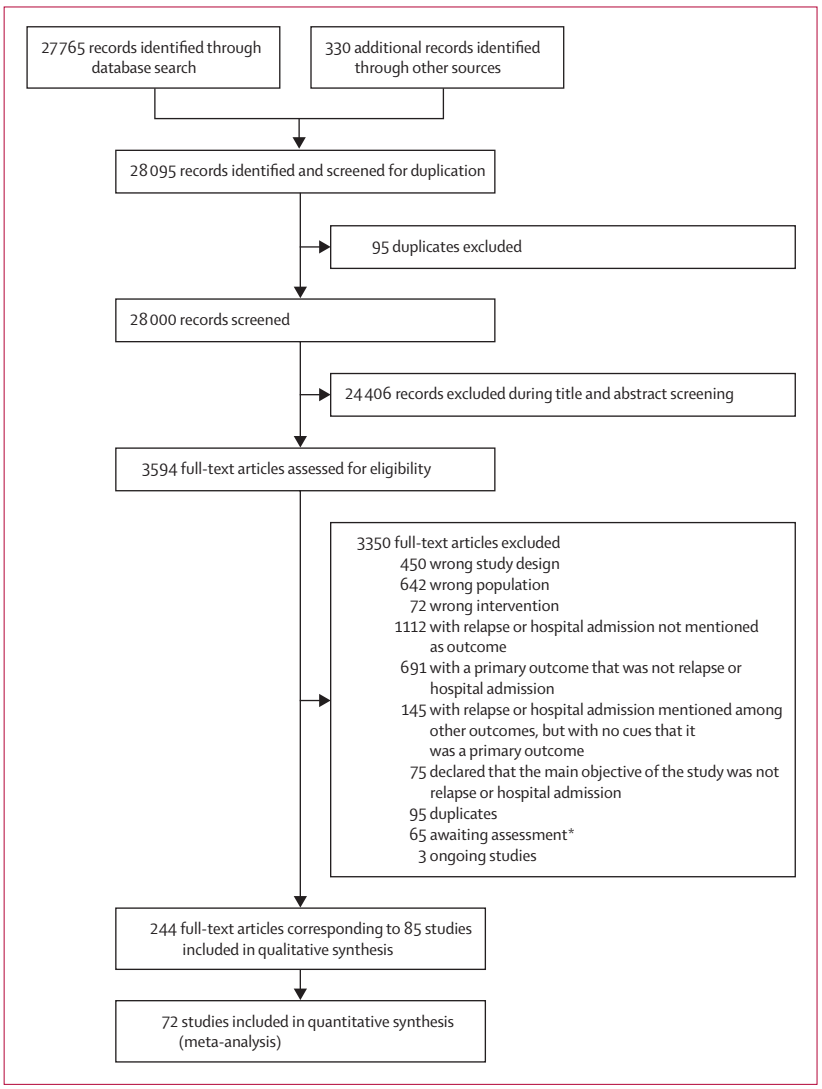


***Figure 1:*** **Study selection**
*No sufficient information about inclusion criteria, or publication in another language that was not possible to translate.

For more on **CINeMA** see http://cinema.ispm.ch

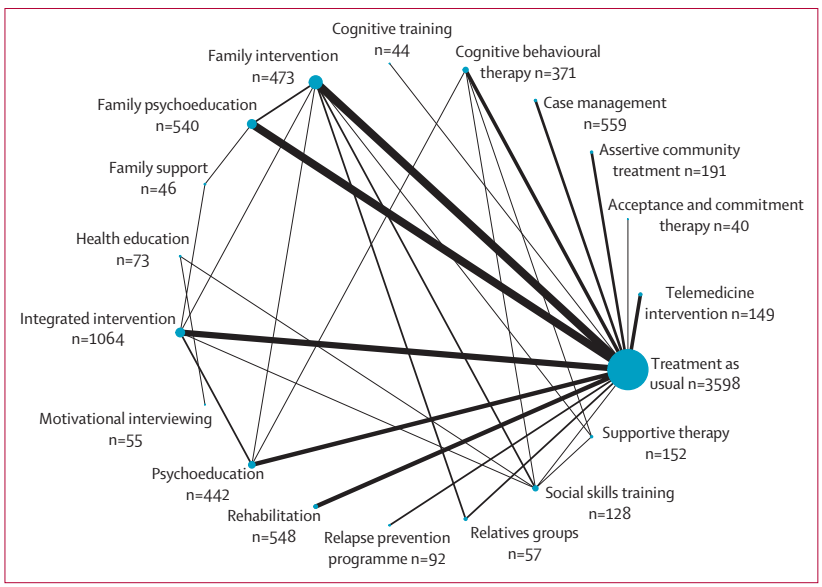


***Figure 2:*** **Network plot of the primary outcome of relapse at 12 months**
The lines link treatments with direct comparisons in trials. The thickness of lines corresponds to the number of trials evaluating the comparison. The size of the nodes corresponds to the number of trials investigating the intervention.

was small, so there might have been a certain level of intransitivity that we were not able to detect.

In the following results discussing the effects of treatments, we focus on network meta-analysis results for which the 95% CI excluded the possibility of no difference between interventions. More details in terms of network plots, forest plots, and league tables are presented in the appendix (pp 49–96). 63 studies with 19 interventions (n=9010 participants; figure 2) contributed to the network meta-analysis of the primary outcome relapse at the primary timepoint of 12 months. ORs compared with treatment as usual (with 95% CIs excluding no effect) and corresponding percentages of participants who relapsed were 0·35 (95% CI 0·24–0·52) with 16% for family interventions, 0·33 (0·14–0·79) with 15% for relapse prevention programmes, 0·45 (0·27–0·75) with 20% for cognitive behavioral therapy, 0·56 (0·39–0·82) with 23% for family psychoeducation, 0·62 (0·44–0·87) with 25% for integrated interventions, and 0·63 (0·42–0·94) with 25% for patient psychoeducation. By contrast, 35% of participants receiving treatment as usual relapsed (figure 3 and figure 4). Family interventions were also associated with a lower probability to relapse than were integrated interventions, patient psychoeducation, rehabilitation, relatives groups, case management, and family support (figure 4). Heterogeneity in estimates between studies of the same comparison was low to moderate; inconsistency in direct and indirect estimates was moderate (appendix pp 97–103).

The confidence intervals for relapse at the secondary timepoints of 6 months and more than 12 months usually overlapped with those of the primary timepoint, meaning similar effects. An exception was for family interventions and family psychoeducation, which were effective at 12 months and longer, but not at 6 months. By contrast, assertive community treatment was effective only at 6 months, but with a broad confidence interval. Cognitive behavioural therapy showed virtually no difference compared with treatment as usual at 6 months and more than 12 months (figure 3).

In the sensitivity and subgroup analyses, the results of the primary outcome were similar to the main analysis, with the exception of assertive community treatment, integrated intervention, patient psychoeducation, and rehabilitation, for which point estimates and confidence intervals showed more variation. For integrated intervention, patient psychoeducation, and rehabilitation, the main analysis showed a superiority in comparison with treatment as usual, but in six or more additional analyses the confidence intervals included the possibility of no difference (figure 5; appendix pp 104–56).

Concerning secondary efficacy outcomes (appendix pp 60–96), almost all interventions were superior to control conditions with 95% CIs excluding no effect except for motivational interviewing, telemedicine, cognitive training, and case management for overall symptoms (31 studies on 15 treatments); integrated interventions, family interventions, and case management for positive symptoms (20 studies on 12 treatments); and assertive community treatment, family psychoeducation, family intervention, case management, and telemedicine for negative symptoms (21 studies on 12 treatments). The probability to drop out due to inefficacy was lower for cognitive behavioural therapy than for treatment as usual (12 studies, eight treatments).

Family interventions were more efficacious than were most other treatments in improving functioning; mindfulness and cognitive behavioural therapy outperformed treatment as usual (24 studies, 14 treatments).

Regarding the acceptability of the interventions, no differences emerged in overall dropout rates, except for a superiority of integrated interventions compared with treatment as usual (59 studies, 19 treatments contributing to the analyses).

Concerning tolerability, integrated interventions were associated with less non-compliance (assessed for this outcome as an adverse event) than was treatment as usual; while relapse prevention programs had a higher probability of non-compliance than did most of the other treatments (22 studies on 13 interventions). Data on other adverse events associated with psychological interventions were scarce and could not be analysed. Death was a very rare event and did not differ between treatments (22 studies with 12 treatments). Insufficient data were available for depressive symptoms, adherence, quality of life, and suicides.

Heterogeneity and inconsistency assessments for secondary outcomes are presented in the appendix

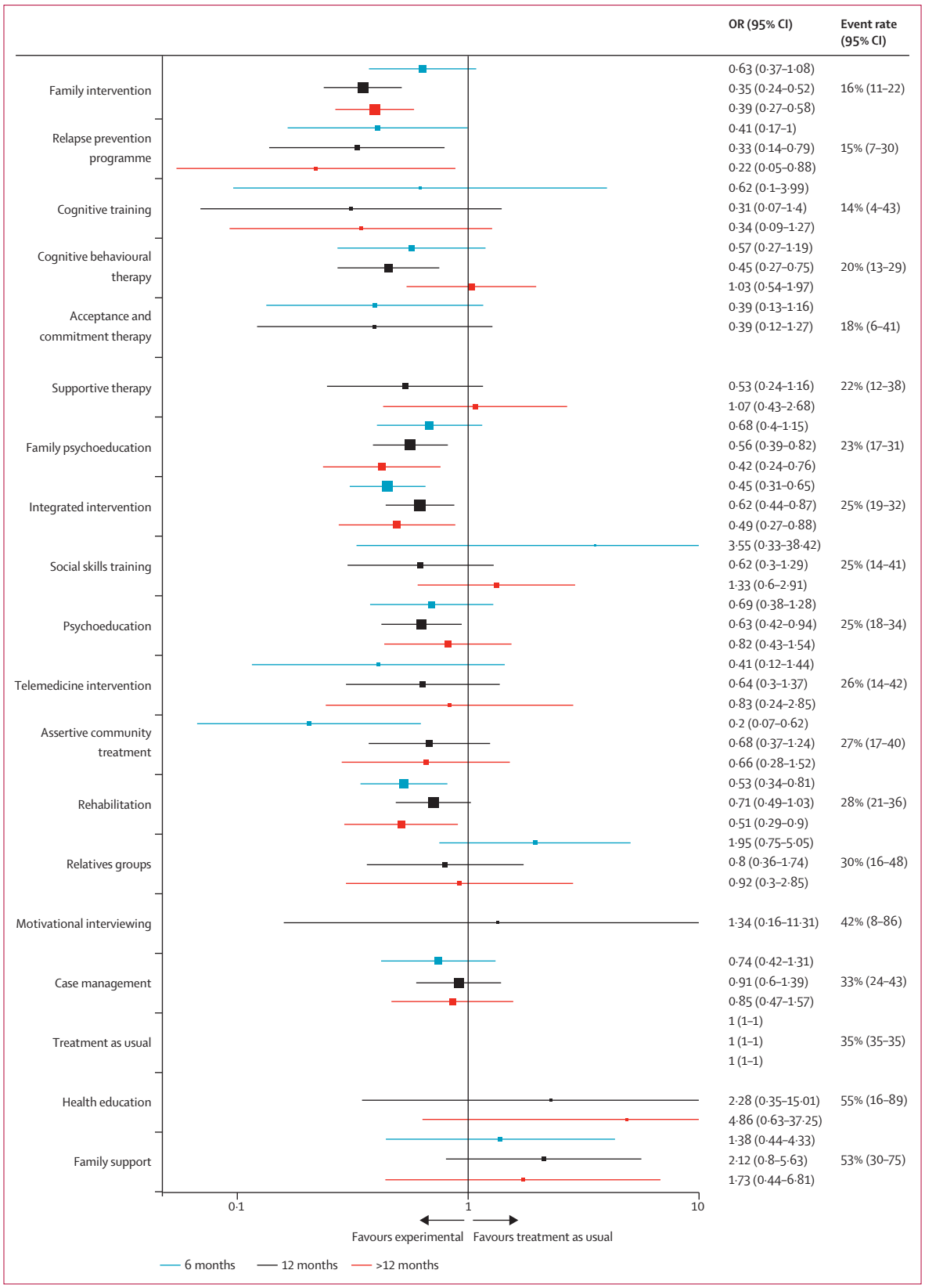


***Figure 3:*** **Forest plots of psychological interventions versus treatment as usual for the primary outcome of relapse at 6 months, 12 months, and more than 12 months**

Treatments are ranked by probability of being the best in preventing relapse (net rank) at the main timepoint (12 months). Reference treatment is treatment as usual. ORs less than 1 are in favour of the psychological intervention. Event rates were calculated from ORs as explained in the appendix (p 3). OR=odds ratios.

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|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| FI | .. | .. | .. | .. | **0·07 (0·01–0·70)** | 0·56 (0·21–1·48) | 2·70 (0·44–16·49) | 0·88 (0·28–2·74) | 0·88 (0·24–3·29) | .. | .. | .. | 0·44 (0·16–1·17) | .. | .. | **0·35 (0·22–0·53)** | .. | .. |
| 1·06 (0·41–2·76) | RPP | .. | .. | .. | .. | .. | .. | .. | .. | .. | .. | .. | .. | .. | .. | **0·33 (0·14–0·79)** | .. | .. |
| 1·12 (0·24–5·30) | 1·06 (0·19–6·03) | CT | .. | .. | .. | .. | .. | .. | .. | .. | .. | .. | .. | .. | .. | 0·31 (0·07–1·40) | .. | .. |
| 0·77 (0·42–1·43) | 0·73 (0·27–2·01) | 0·69 (0·14–3·36) | CBT | .. | 1·41 (0·60–3·30) | .. | .. | 0·26 (0·06–1·14) | 0·10 (0·00–1·91) | .. | .. | .. | .. | .. | .. | **0·45 (0·26–0·79)** | .. | .. |
| 0·89 (0·26–3·05) | 0·84 (0·19–3·61) | 0·79 (0·12–5·31) | 1·15 (0·32–4·12) | ACTP | .. | .. | .. | .. | .. | .. | .. | .. | .. | .. | .. | 0·39 (0·12–1·27) | .. | .. |
| 0·66 (0·29–1·50) | 0·62 (0·19–1·99) | 0·58 (0·11–3·17) | 0·85 (0·42–1·70) | 0·74 (0·18–3·02) | ST | .. | .. | 1·14 (0·41–3·21) | .. | .. | .. | .. | .. | .. | .. | .. | .. | .. |
| 0·62 (0·37–1·04) | 0·59 (0·23–1·52) | 0·55 (0·12–2·60) | 0·80 (0·43–1·50) | 0·70 (0·20–2·40) | 0·95 (0·40–2·24) | FP | .. | .. | .. | .. | .. | .. | .. | .. | .. | **0·56 (0·38–0·82)** | .. | 0·29 (0·05–1·76) |
| **0·56 (0·34–0·94)** | 0·53 (0·21–1·36) | 0·50 (0·11–2·35) | 0·73 (0·40–1·34) | 0·64 (0·19–2·16) | 0·86 (0·37–2·00) | 0·91 (0·55–1·50) | II | 0·24 (0·04–1·40) | 0·91 (0·41–2·04) | .. | .. | .. | .. | .. | .. | **0·64 (0·45–0·93)** | .. | **0·28 (0·10–0·84)** |
| 0·56 (0·26–1·21) | 0·53 (0·17–1·65) | 0·50 (0·09–2·65) | 0·73 (0·35–1·52) | 0·63 (0·16–2·52) | 0·86 (0·39–1·86) | 0·90 (0·40–2·04) | 0·99 (0·45–2·20) | SST | .. | .. | .. | .. | .. | .. | .. | 0·55 (0·17–1·78) | 0·27 (0·05–1·55) | .. |
| **0·56 (0·33–0·95)** | 0·52 (0·20–1·37) | 0·50 (0·10–2·34) | 0·72 (0·38–1·36) | 0·63 (0·18–2·17) | 0·85 (0·36–2·02) | 0·89 (0·52–1·54) | 0·98 (0·61–1·59) | 0·99 (0·44–2·25) | PE | .. | .. | .. | .. | .. | .. | 0·68 (0·43–1·08) | .. | .. |
| 0·55 (0·23–1·30) | 0·52 (0·16–1·66) | 0·49 (0·09–2·64) | 0·71 (0·28–1·78) | 0·62 (0·15–2·51) | 0·84 (0·28–2·49) | 0·88 (0·38–2·07) | 0·97 (0·42–2·25) | 0·98 (0·34–2·82) | 0·99 (0·42–2·34) | TI | .. | .. | .. | .. | .. | 0·64 (0·30–1·37) | .. | .. |
| 0·51 (0·25–1·06) | 0·49 (0·17–1·41) | 0·46 (0·09–2·31) | 0·66 (0·30–1·46) | 0·58 (0·15–2·17) | 0·78 (0·29–2·10) | 0·83 (0·41–1·69) | 0·91 (0·45–1·83) | 0·92 (0·36–2·36) | 0·92 (0·45–1·91) | 0·94 (0·35–2·49) | ACT | .. | .. | .. | .. | 0·68 (0·37–1·24) | .. | .. |
| **0·49 (0·29–0·85)** | 0·47 (0·18–1·21) | 0·44 (0·09–2·07) | 0·64 (0·34–1·20) | 0·56 (0·16–1·91) | 0·75 (0·32–1·79) | 0·80 (0·47–1·35) | 0·88 (0·53–1·45) | 0·88 (0·39–2·00) | 0·89 (0·51–1·54) | 0·90 (0·38–2·12) | 0·96 (0·47–1·96) | RE | .. | .. | .. | 0·71 (0·49–1·03) | .. | .. |
| **0·44 (0·20–0·97)** | 0·41 (0·13–1·34) | 0·39 (0·07–2·13) | 0·57 (0·22–1·43) | 0·50 (0·12–2·03) | 0·67 (0·23–1·99) | 0·71 (0·30–1·67) | 0·78 (0·33–1·82) | 0·78 (0·27–2·23) | 0·79 (0·33–1·89) | 0·80 (0·27–2·39) | 0·85 (0·32–2·30) | 0·89 (0·37–2·11) | RG | .. | .. | 0·90 (0·37–2·23) | .. | .. |
| 0·26 (0·03–2·23) | 0·25 (0·02–2·46) | 0·23 (0·02–3·15) | 0·34 (0·04–2·85) | 0·29 (0·03–3·35) | 0·40 (0·05–3·41) | 0·42 (0·05–3·64) | 0·46 (0·05–3·98) | 0·46 (0·06–3·44) | 0·47 (0·05–4·09) | 0·47 (0·05–4·58) | 0·51 (0·06–4·65) | 0·53 (0·06–4·59) | 0·59 (0·06–5·70) | MI | .. | .. | 0·59 (0·22–1·60) | .. |
| **0·38 (0·22–0·68)** | **0·36 (0·14–0·96)** | 0·34 (0·07–1·63) | **0·50 (0·26–0·96)** | 0·43 (0·12–1·51) | 0·59 (0·24–1·42) | 0·62 (0·35–1·09) | 0·68 (0·39–1·17) | 0·68 (0·29–1·59) | 0·69 (0·39–1·24) | 0·70 (0·29–1·68) | 0·75 (0·36–1·56) | 0·78 (0·44–1·37) | 0·87 (0·36–2·13) | 1·47 (0·17–12·96) | CM | 0·91 (0·60–1·39) | .. | .. |
| **0·35 (0·24–0·52)** | **0·33 (0·14–0·79)** | 0·31 (0·07–1·40) | **0·45 (0·27–0·75)** | 0·39 (0·12–1·27) | 0·53 (0·24–1·16) | **0·56 (0·39–0·82)** | **0·62 (0·44–0·87)** | 0·62 (0·30–1·29) | **0·63 (0·42–0·94)** | 0·64 (0·30–1·37) | 0·68 (0·37–1·24) | 0·71 (0·49–1·03) | 0·80 (0·36–1·74) | 1·34 (0·16–11·31) | 0·91 (0·60–1·39) | TAU | .. | .. |
| 0·15 (0·02–1·02) | 0·14 (0·02–1·15) | 0·14 (0·01–1·52) | 0·20 (0·03–1·31) | 0·17 (0·02–1·59) | 0·23 (0·03–1·56) | 0·25 (0·04–1·68) | 0·27 (0·04–1·83) | 0·27 (0·05–1·55) | 0·28 (0·04–1·88) | 0·28 (0·04–2·13) | 0·30 (0·04–2·15) | 0·31 (0·05–2·11) | 0·35 (0·05–2·65) | 0·59 (0·22–1·60) | 0·40 (0·06–2·75) | 0·44 (0·07–2·88) | HE | .. |
| **0·16 (0·06–0·47)** | **0·16 (0·04–0·57)** | **0·15 (0·02–0·88)** | **0·21 (0·07–0·64)** | **0·19 (0·04–0·85)** | **0·25 (0·07–0·87)** | **0·26 (0·10–0·72)** | **0·29 (0·11–0·75)** | **0·29 (0·09–0·98)** | **0·30 (0·11–0·83)** | 0·30 (0·09–1·04) | 0·32 (0·10–1·01) | **0·33 (0·12–0·95)** | 0·37 (0·11–1·30) | 0·63 (0·06–6·56) | 0·43 (0·15–1·24) | 0·47 (0·18–1·25) | 1·07 (0·13–8·93) | FS |

***Figure 4:*** **League table of the primary outcome of relapse at 12 months**

Treatments are ranked by probability of being the best in preventing relapse (net rank). Results from the network meta-analysis (mixed [network] and indirect comparisons) are presented in the lower left triangle and results from pairwise meta-analyses (direct comparisons) are presented in the upper right triangle. Significant results are presented in bold. Relative treatment effects are measured by odds ratios along with their 95% CIs. The colours of the cells in the lower triangle represent the confidence in the estimate results obtained with CINeMA: blue indicates moderate confidence, yellow indicates low confidence, and red indicates very low confidence. ACT=assertive community treatment. ACTP=acceptance and commitment therapy. CBT=cognitive behavioural therapy. CM=case management. CT=cognitive training. FI=family intervention. FP=family psychoeducation. FS=family support. HE=health education. II=integrated intervention. MI=motivational interviewing. PE=patient psychoeducation. RE=rehabilitation. RG=relatives groups. RPP=relapse prevention programme. ST=supportive therapy. SST=social skills training. TAU=treatment as usual. TI=telemedicine.

(pp 97–103). For many secondary outcomes the networks were thin and the power was low, and therefore there might be an inconsistency that we were not able to detect. We found no indication of small-study effects (comparison-adjusted funnel plot of the primary outcome in the appendix, p 157; Harbord test p=0·56).

Judgements about confidence in the estimates (CINeMA) ranged from moderate to very low, meaning that further research is very likely to affect our confidence in the estimate of effect and is likely to change the estimate (figure 4; appendix pp 158–174).

## Discussion

To our knowledge, we did the first network meta-analysis investigating psychosocial and psychological interventions for relapse prevention. We analysed 20 interventions reported in 72 randomised controlled trials with 10 364 participants.

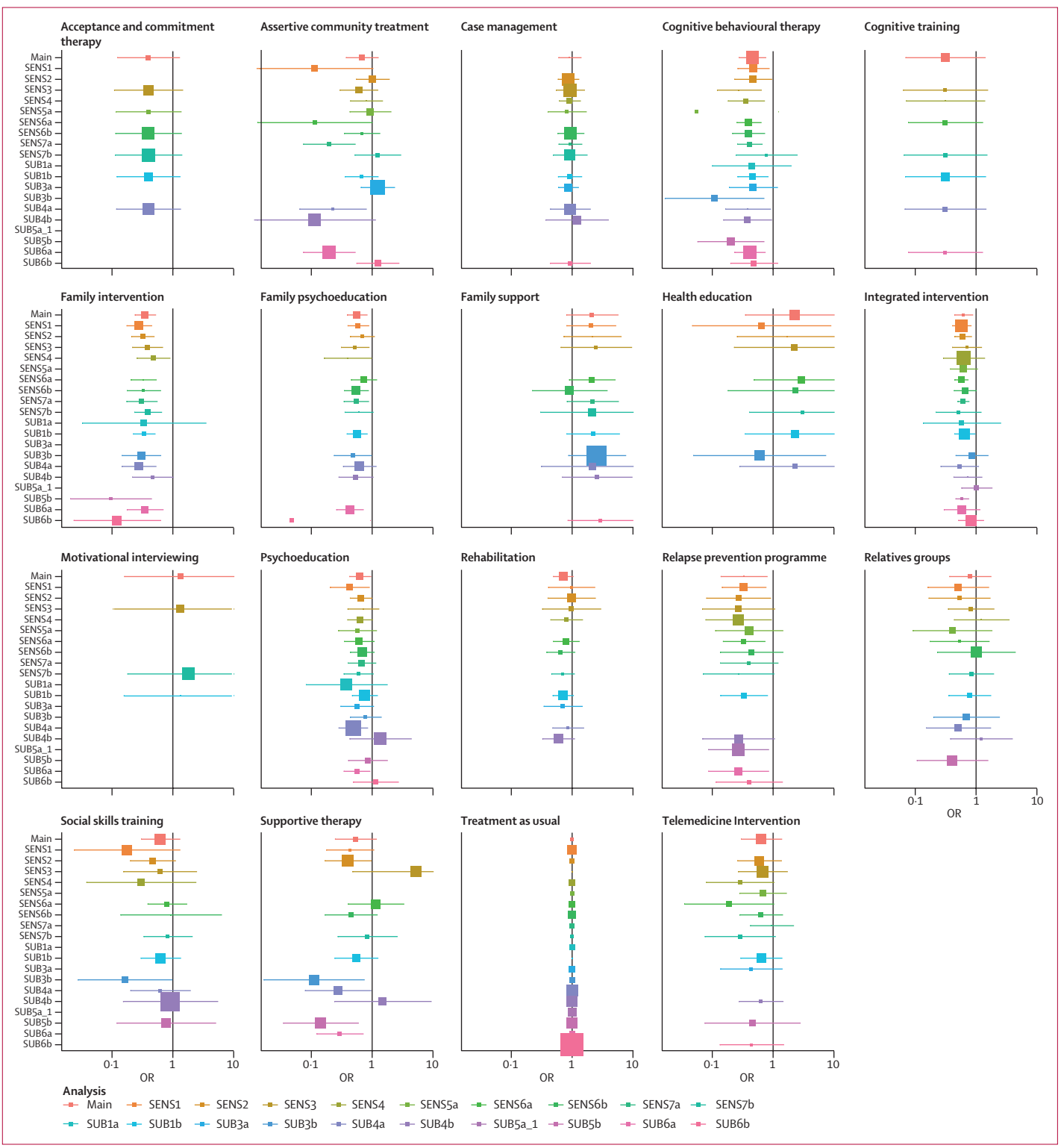
We found that family interventions, family psychoeducation, cognitive behavioral therapy, patient psychoeducation, integrated interventions, and relapse prevention programmes were superior to standard care alone in preventing relapses at 12 months.

Overall, the interventions showed consistent patterns at the three time points considered, because confidence intervals overlapped broadly, with a few notable exceptions. Family interventions and family psychoeducation were not more efficacious than treatment as usual at 6 months, but only after 1 year. This result is consistent with the Cochrane review by Pharoah and colleagues.[7] Assertive community treatment was efficacious only at 6 months

***Figure 5:*** **Forest plots of sensitivity and subgroup analyses**

Reference treatment is treatment as usual. ORs less than 1 are in favour of the psychological intervention. OR=odds ratios. Main=main analysis. SENS1=exclusion of studies in which the outcome assessor was not masked. SENS2=exclusion of studies that presented only completer analysis. SENS3=exclusion of studies with high risk of bias in the overall domain. SENS4=exclusion of studies with researchers' allegiance. SENS5a=patients who dropped out from the study were considered as having relapsed. SENS6a=relapse defined with operationalised criteria. SENS6b=relapse defined as hospital admissions. SENS7a=exclusion of studies in which relapse or hospital admission was not defined explicitly as the primary outcome but on the basis of our judgement (only explicit). SENS7b=studies in which relapse or hospital admission was not defined explicitly as the primary outcome but on the basis of our judgement analysed alone (excluding explicit). SUB1a=studies done in patients with first-episode schizophrenia. SUB1b=studies done in patients with chronic schizophrenia. SUB3a=intervention done in individual setting. SUB3b=intervention done in non-individual setting (group, family). SUB4a=status inpatient (at enrolment in the study). SUB4b=status outpatient (at enrolment in the study). SUB5a_1=low number of sessions. SUB5b=high number of sessions. SUB6a=high baseline severity. SUB6b=low baseline severity.

and cognitive behavioural therapy was efficacious only at 1 year, but not in the longer term. Notably, results at different timepoints were often from different studies, and fewer studies reported data at 6 months and more than 1 year compared with at 1 year, leading to lower power at these secondary timepoints.



Family interventions were also efficacious in improving other outcomes such as symptoms of schizophrenia and functioning. Therefore, the prevention effect on relapse could be mediated by other factors such as reduction in symptoms, better functioning, direct involvement of family members, and better compliance. Family members might become more able to manage crises, reducing hospital admissions. A simpler intervention in the form of family psychoeducation was also effective in preventing relapses and improving symptoms. Thus, in the absence of resources, simple family psychoeducation might be offered as a minimum solution. Both family interventions and family psychoeducation need some time to take effect, reducing the risk of relapse only after 1 year. By contrast, the mere provision of support for relatives or family had no effect. The effects of different kinds of family interventions on relapse are under investigation in an ongoing network meta-analysis.[27]

Patient psychoeducation was more effective than was treatment as usual at 12 months, but not at 6 months or more than 12 months, but with broadly overlapping confidence intervals. In the Cochrane review by Xia and colleagues,[6] patient psychoeducation was efficacious in preventing relapse after 1 year. This pairwise meta-analysis had broader inclusion criteria (which is not possible with a network meta-analysisNMA in order not to break the transitivity assumption) and therefore more data. Furthermore, we found patient psychoeducation to be effective in reducing symptoms and improving adherence when compared with treatment as usual.

Cognitive behavioural therapy was efficacious in reducing relapse at 12 months and in improving many secondary outcomes (overall, positive, and negative symptoms; adherence; and functioning). The benefit in reduction of relapse in the longer term is unclear, consistent with the results of Jones and colleagues.[8] Cognitive behavioural therapy is not specifically designed for relapse prevention; its primary goal is to reduce persistent psychotic symptoms, for which it is effective.[28] Other modules of cognitive behavioural therapy could be developed to improve its effect for relapse prevention in the longer term.

Integrated interventions combine different components as a treatment. Results were robust across timepoints for relapse and showed efficacy in primary and secondary outcomes. However, the implications for clinical practice are unclear, because it cannot be deduced whether integrated interventions are effective because they include more components or because certain components are deemed particularly effective. A component network meta-analysis design could help to ascertain the role of the specific elements of the integrated interventions.

Specific relapse prevention programmes focus on relapse prevention by monitoring early symptoms of relapse. Results were promising, but little evidence was available (two studies with 92 participants).

Psychosocial interventions such as assertive community treatment, case management, and rehabilitation aim at providing structure to the life of the patient outside of the hospital, by visiting the patient at home, providing a reference figure for service organisation, or offering rehabilitation activities. Rehabilitation had promising results in preventing relapse; assertive community treatment reduced the risk of relapse at 6 months, while for case management the confidence intervals include the possibility of no difference with treatment as usual (only three studies). These results are consistent with previous broader reviews that found assertive community treatment effective in preventing relapse,[29] and no protective effect for case management.[30]

Other psychosocial interventions did not reduce the risk of relapse. For some of them, this might not be surprising, because they are either designed with a different focus than relapse prevention (eg, social skills training), or little evidence was available (eg, cognitive training or telemedicine).

Overall, results on efficacy-related secondary outcomes showed the same patterns as the primary outcome, relapse.

Whether psychotherapy can cause side effects is an important question,[12,31] but still rarely investigated. On the basis of our data, we could not draw conclusions on the tolerability of the investigated interventions. Potential side effects can be more easily monitored in observational studies that focus more on the process of psychotherapy, rather than the outcome, as is the case with randomised controlled trials. Trials have many methodological challenges, and investigation of weakly defined outcomes might be very difficult.

Our findings have the following limitations. Firstly, the available data for many comparisons are based on few studies (in some cases just one or two studies), leading to thinly connected networks and low statistical power to detect possible differences. Therefore, the results should be interpreted with caution, and for this reason hierarchies based on p values and direct comparisons between interventions were used only for presentation purposes, but not interpreted.

Secondly, risk of bias in the included studies was classified as some concerns or high, leading to mainly low confidence in the estimates evaluated with CINeMA. Masking of therapist and patients is not possible in studies on psychological interventions, introducing an unavoidable source of bias.

Thirdly, although we applied stringent inclusion criteria and identified no clear transitivity problems, there was heterogeneity and inconsistency for some outcomes. We explored potential effect modifiers, but found no evident role for any of the moderators investigated. By contrast, results were generally robust across additional analyses. We planned to investigate the role of different definitions of relapse, but because relapse was often poorly defined this analysis was not

possible, except for the separate analysis of readmission to hospital.

Fourth, in all the included randomised controlled trials, psychological interventions were offered in addition to pharmacological treatment. Details on medication received and doses are very rarely provided, so that the roles of the treatments are difficult to disentangle. If randomisation ensures that characteristics of patients and potential confounders, such as pharmacological treatment received, are equally distributed between the study arms, randomisation cannot address any potential modifying effect of pharmacological treatment received on the effect of the added psychological and psychosocial intervention. Findings about the included psychological and psychosocial interventions must be interpreted as the effects of the interventions provided in addition to pharmacotherapy.

To overcome these limitations, high quality randomised controlled trials need to be done, reporting on patient drug therapy in detail and providing an operationalised definition of relapse. These trials, together with studies of other designs, should also investigate the mechanisms and specific processes of change underlying the relapse preventive effects of the interventions, which is important for their scalability and sustainability in routine care.

Finally, although patient psychoeducation, integrated interventions, and relapse prevention programmes were effective for the primary outcome, there was considerable variability in different subgroup and sensitivity analyses. By contrast, results for family interventions, family psychoeducation and cognitive behavioural therapy were robust, and their nodes were well connected in the networks. For this reason, although our results demonstrate that many psychological interventions can play a role in the prevention of relapse in patients with schizophrenia, policy makers and clinicians should consider giving priority to family interventions, family psychoeducation, and cognitive behavioural therapy when allocating resources and planning maintenance treatment for patients with schizophrenia.

#### Contributors

IB, AR, and SL designed the study, with input from GP-W, CB, TAF, and GS. IB set up the database, with help from JS-T. IB, AR, HG-M, HW and DW screened the literature search, acquired reports of the relevant trials, identified multiple publications of individual studies, selected included studies, and extracted data. IB contacted trial investigators for additional information and did the statistical analyses, with inputs from SS, SL and GS. IB, AR, SL, and GS analysed and interpreted the data. W-PH provided input to study design and results interpretation from patients' perspective. IB and AR verified the underlying data. IB and SL wrote the draft and the final version of the manuscript. All authors critically reviewed the report for important intellectual content and approved the final submitted version. All authors had full access to all the data in the study and accept responsibility to submit for publication.

#### Declaration of interests

In the past 3 years, SL has received honoraria for service as a consultant or adviser for Alkermes, Angelini, Gedeon Richter, Lundbeck, Recordati, ROVI, Sandoz, and TEVA; and for lectures from Angelini, Eisai, Gedeon Richter, Janssen, Johnson and Johnson, Lundbeck, Merck Sharpp and Dome, Otsuka, Recordati, SanofiAventis, Sunovion, and Medichem. TAF reports grants and personal fees from Mitsubishi-Tanabe, personal fees from MSD, and grants and personal fees from Shionogi, outside of the submitted work. Additionally, TAF has a patent 2020-548587 concerning smartphone CBT applications pending, and intellectual properties for Kokoro-application licensed to Mitsubishi-Tanabe. All other authors declare no competing interests.

#### Data sharing

Please contact the corresponding author if you would like to see any data that are not included in the Article or the Appendix.

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