Interventions and Transition in Youth at Risk of Psychosis:
A Systematic Review and Meta-Analyses

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ABSTRACT

Objective: The primary objective of this systematic review and meta-analyses was to summarize the impact of all reported treatments on transition to psychosis in high-risk samples.

Data Sources: PsycINFO, Embase, CINAHL, EBM, and MEDLINE online databases were searched from inception to May 2017 using the keywords *psychosis*, *risk*, and *treatment* with no geographical, date, or language restrictions.

Study Selection: A total of 38 independent studies met the inclusion criteria: conducted a treatment study in a sample at high risk for psychosis and reported on transition to psychosis as an outcome.

Data Extraction: The following data were extracted: study characteristics (eg, sample size), participant characteristics (eg, mean age), and clinical outcome data (eg, number and percentage of patients transited for each intervention group at each time-point and transition assessment employed). Data were analyzed using random-effects pairwise meta-analysis (to explore differences between treatment and controls) and multivariate network meta-analyses (NMAs; to explore differences between treatment types on transition) and were reported as risk ratios (RR).

Results: In pairwise meta-analyses, cognitive-behavioral therapy (CBT) studies were associated with a significant reduction in transition compared with controls at 12-month and 18-month follow-up (RR = 0.57; 95% CI, 0.35–0.93; $I^2 = 7\%$; $P = .02$ vs RR = 0.54; 95% CI, 0.32–0.92; $I^2 = 0\%$; $P = .02$). In the NMAs, integrated psychological therapy, CBT, supportive therapy, family therapy, needs-based interventions, omega-3, risperidone plus CBT, ziprasidone, and olanzapine were not significantly more effective at reducing transition at 6 and 12 months relative to each other.

Conclusions: This systematic review and pairwise meta-analyses demonstrated a reduced risk for transition favoring CBT at 12 and 18 months. No interventions were significantly more effective at reducing transition compared with all other interventions in the NMAs. NMA results should be interpreted with caution due to the small sample size.

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Between 17% and 28% of those identified as being at clinical high risk (CHR) for psychosis will have a first psychotic episode within the first year.[1] In a recent meta-analysis,[2] attenuated psychotic symptoms and global functioning were 2 factors associated with transition to psychosis, followed by negative symptoms. Longer duration of untreated psychosis has also been reported to lead to poorer outcomes, including functional deficits[3,4] and greater psychotic symptoms.[5,6] The morbidity associated with frank psychotic illnesses is well recognized,[7] with general consensus that effective interventions are necessary to prevent the onset of psychosis.[8–10]

Accordingly, transition to a psychotic disorder has been the primary outcome in the majority of randomized and observational intervention studies in those at CHR for psychosis. A variety of interventions (eg, antipsychotics, cognitive behavioral therapy [CBT], omega-3) have been tested, but most of these interventions have not been efficacious over control treatment or treatment as usual at reducing transition rates. There is a need for a more comprehensive search and assessment of the impact of interventions on transition to psychosis to inform both clinical practice and future trials.

Presently, to the best of our knowledge, only 2 aggregate pairwise meta-analyses have examined the impact of treatment interventions on transition to psychosis in those at CHR for psychosis. The first review[11] found an effect for CBT on reducing transition at 12 months, and the latter[12] found that "CBT-informed" treatment was associated with a reduced risk of transition to psychosis at 6 months, 12 months, and long-term follow-up. Both reviews focused mainly on the efficacy of CBT; however, interventional studies in CHR samples have increased considerably and encompass newer treatments such as *N*-methyl-D-aspartate receptor (NMDAR) modulator interventions (glycine and D-serine), cognitive remediation therapy (CRT), and omega-3.[13–15] Our review expands on the previous reviews, first by systematically ascertaining more than 4 times the number of intervention studies and examining their impact on transition. Second, we performed the recommended two-step approach of first conducting a traditional pairwise meta-analysis followed by a network meta-analysis (NMA).[16] The benefit of an NMA is that it allows for indirect comparisons between treatment arms that have not been compared before in a head-to-head fashion[17] (eg, CBT to family therapy to antipsychotics) by using common comparators (eg, placebo, supportive therapy, needs-based interventions), and the results can offer a framework for clinical decision making.[16] However, NMAs are often difficult to understand and subject to bias, which may lead to a misinterpretation of results,[17] and some argue that it remains unclear whether or not NMAs

Clinical Points

- Treatments for those at clinical high risk for psychosis have been increasing, but the most effective treatment for reducing transition has not yet been established.
- In pairwise meta-analyses, cognitive-behavioral therapy (CBT) studies were associated with a significant reduction in transition compared to controls at 12-month and 18-month follow-up.
- If a patient presents with being at risk for psychosis, clinicians should consider offering CBT to help reduce the risk of a first episode.

improve patient care and outcomes.[16] The benefit of using a traditional pairwise meta-analysis is that it allows you to compare treatments to controls and is easier to comprehend and decipher for clinicians.[16]

By including additional studies, new treatment interventions, a more comprehensive systematic search of the literature, and a novel analysis, the evidence base on treatment interventions and their impact on transition to psychosis in CHR youth will be enhanced.

METHODS

Protocol

A protocol was registered a priori for this systematic review and meta-analyses (PROSPERO [International Prospective Register of Systematic Reviews] number: CRD42017077963). All processes adhered to Preferred Reporting Item for Systematic Reviews and Meta-Analyses (PRISMA) guidelines and Meta-analysis of Observational Studies in Epidemiology (MOOSE) guidelines.[18–21] A PRISMA checklist is available for both the pairwise meta-analyses and NMAs; see Supplementary Search 1 for details.[22]

Objective

The primary objective of this systematic review and meta-analyses was to summarize the impact of all reported interventions on transition to psychosis.

Data Sources and Search Strategy

MEDLINE, PsycINFO, Embase, CINAHL (Cumulative Index to Nursing and Allied Health Literature), and EBM (Evidence-based Medicine) online databases were systematically searched up to May 2017, using no geographical, date or language restrictions. The detailed search strategies are presented in Supplementary Search 1. Title and abstract screening were followed by a more comprehensive, full-text screening (based on inclusivity), which was performed independently and in duplication by 2 reviewers (M.S.F. and P.T.). All references lists of articles meeting the inclusion criteria were hand-searched for additional relevant articles. Further, to broaden the search, additional searches were performed as follows: (1) Scopus (http://www.scopus.com) using the keywords *psychosis risk* and *treatment*, (2) Clinicaltrials.gov registry using the keywords *psychosis risk* and *treatment*, and (3) The International Clinical Trials Registry Platform (http://apps.who.int/trialsearch/) using the keywords *psychosis* and *risk*.

Selection Criteria

Inclusion criteria for this systematic review were as follows: (1) studies including participants at risk of psychosis, including attenuated psychotic symptom syndrome (requires the presence of at least 1 attenuated psychotic symptom, which has begun or worsened in the past year), genetic risk and deterioration (combination of both functional decline and genetic risk), brief intermittent psychotic syndrome (requires the presence of any 1 or more psychotic symptoms that are too brief to meet diagnostic criteria for psychosis), early initial prodromal state (requires the presence of basic symptoms or a functional decline in combination with perinatal complications or genetic risk), or schizotypy; (2) studies including treatments in an observational or experimental setting; (3) studies reporting transition or conversion to psychosis; and (4) studies reporting a mean age of participants between 12 and 30 years. Studies were excluded if they employed an unsuitable study design (eg, case reports, review articles, editorials with insufficient study information) or did not involve an intervention (eg, treatment). Reconciliation of any discrepancies were resolved by a third reviewer (D.J.D. or J.A.).

Data Extraction

Data were extracted from all included studies, completed independently and in duplication by 2 reviewers (M.S.F. and P.T.), and verified by a third reviewer (D.J.D.). The following data were extracted: study characteristics (first author, publication year, country, study design, CHR sample size, number of study centers, CHR criterion used, rate of attrition for intervention and control groups, method of imputation used, severe adverse events reported), participant characteristics (mean ± SD age, number and percentage of male patients), treatment characteristics (number of participants allocated to each intervention and control group, type of intervention, type of control, duration, study endpoint), and clinical outcome data (number and percentage of patients transited for each intervention group at each time-point and transition assessment employed). Percentage transitioned was calculated and extracted accordingly if not present in the article. Crude risk ratios (RRs) and number-needed-to-treat were derived using the percent transitioned in each intervention/control group and used in the qualitative synthesis.

Risk-of-Bias Assessment

Cochrane's tool for assessing risk-of-bias[23] for randomized studies was used to evaluate study quality, using Review Manager[24] (RevMan) version 5.1 (training.cochrane.org/). Further, for nonrandomized studies, the Risk-of-Bias In Nonrandomized Studies of Interventions (ROBINS-I)[25] was used to evaluate quality of evidence. In the NMAs, to assess the quality of evidence associated with comparisons,

the level of bias present in most trials was estimated using the blinding of outcome assessments and weighted according to the number of studies in each comparison using colored edges (green = low risk, yellow = unclear risk, red = high risk) and the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach[26] was used to evaluate the quality of evidence associated with the results in the NMAs at each time point.

Data Synthesis and Analysis

The κ statistic was used in the title/abstract screening phase to assess agreement between reviewers. Treatments were combined in both the pairwise meta-analyses and NMAs to account for similarities in design. Specifically, D-serine and glycine were combined as *N*-methyl-D-aspartate-receptor (NMDAR) modulators, as they are both amino acids that serve as neuromodulators acting as coagonists on the NMDAR with glutamate.[27,28] Further, enhanced care, treatment as usual, community care, monitoring, and needs-focused interventions were merged as needs-based interventions (NBI). Only randomized control trials were included in meta-analyses, while observational studies were included in the qualitative synthesis. Random-effects models in the pairwise meta-analyses and NMAs were used to account for differences between studies because of study design, dose, CHR criteria, and the idiosyncratic treatment strategies. Last, the principal summary measure utilized in all analyses were RRs.

For the primary analysis, a DerSimonian and Laird[29] random-effects pairwise model was used to derive pooled transition RR estimates for individual treatments types with a minimum of 2 trials (eg, 3 omega-3 trials) compared with the controls (eg, placebo). In the pairwise analysis, transition was stratified by available time points (eg, 6-months, 12-months, 18-months). Pairwise comparisons were performed in RevMan 5.1.[24] Statistical heterogeneity was evaluated using the I^2 statistic, where $I^2 \geq 50\%$ indicated moderate heterogeneity and $I^2 \geq 75\%$ was deemed high heterogeneity.

For the secondary analysis, the White[30] and Higgins[31] random-effects multivariate NMA assuming consistency, common heterogeneity across all comparisons in the network, and inverse-variance probability weighting[32,33] was used to examine and directly compare treatment intervention effects in RCTs. This method was chosen to account for studies with multiple treatment arms (> 2)[34] as it appropriately accounts for correlations between RRs in multiarm RCTs. Exponential format was applied for display in the forest plots produced. Due to the heterogeneity of study endpoints, only studies with transition rates reported at either 6-month, 12-month, or long-term follow-ups were included. Observational study designs and studies with additional participants not classified as CHR (eg, schizotypy) were excluded from the NMA. Both a global test for inconsistency[34] and inconsistency plots assuming loop-specific heterogeneity were produced to determine if inconsistency existed in the NMA.[35–38] These effects were potentially mitigated a priori with the use of inclusion criteria employed at the screening phases (eg, age). Furthermore, to investigate the most effective interventions compared with a better hypothetical treatment, surface under the cumulative ranking curve (SUCRA) was plotted. The closer the curve arches to 1, the higher the probability of efficacy.[35,39] Network comparison-adjusted funnel plots[35] were used to assess publication bias by ordering the interventions as active treatment versus controls. Last, a sensitivity analysis was performed in both the 6- and 12-month NMAs by dropping studies that had a high risk-of-bias for blinding of outcomes based on Cochrane's tool for assessing risk-of-bias.[23] We analyzed NMA data using Stata version 13 (StataCorp LLC: College Station, Texas), and graphical illustrations of the network evidence utilized the graphical toolset called "networkplot."[35] All statistical analyses used an $\alpha < .05$ for statistical significance.

RESULTS

Search Yield

Our search strategy rendered 10,344 citations. Of those, 8,983 unique titles and abstracts were screened in duplication. Agreement between title and abstract reviewers was high for study inclusion (κ = 0.88). Overall, 204 full-text articles were screened and 45 articles[13–15,28,40–80] fit our inclusion criteria for the systematic review. We identified 38 unique studies,[13–15,40–43,46–50,52–64,66–69,71–74,76–78] with 2 studies published in 1 article,[28] and 8 articles[44,45,51,65,70,75,79,80] with a duplicate study population (see Figure 1).

Study and Participant Characteristics

Study design varied and included 21 RCTs, 9 open-label designs, 7 naturalistic design, and 1 regression discontinuity design, all outlined in Table 1. The majority of the studies were performed in North America (15), followed by Europe (11), Asia (7), and Australia (4); one was a multinational study. This review included a total of 3,489 CHR participants with a mean age of 19.9 years, and 53.9% were male. Sample size and mean age ranged from 8 to 304 participants and 15.3 to 27.1 years, respectively. The most common measure used to identify transition to psychosis was the Structured Interview of Psychosis-risk Syndromes (SIPS) (19 studies), followed by the Comprehensive Assessment of At-risk Mental States (CAARMS) (12 studies).

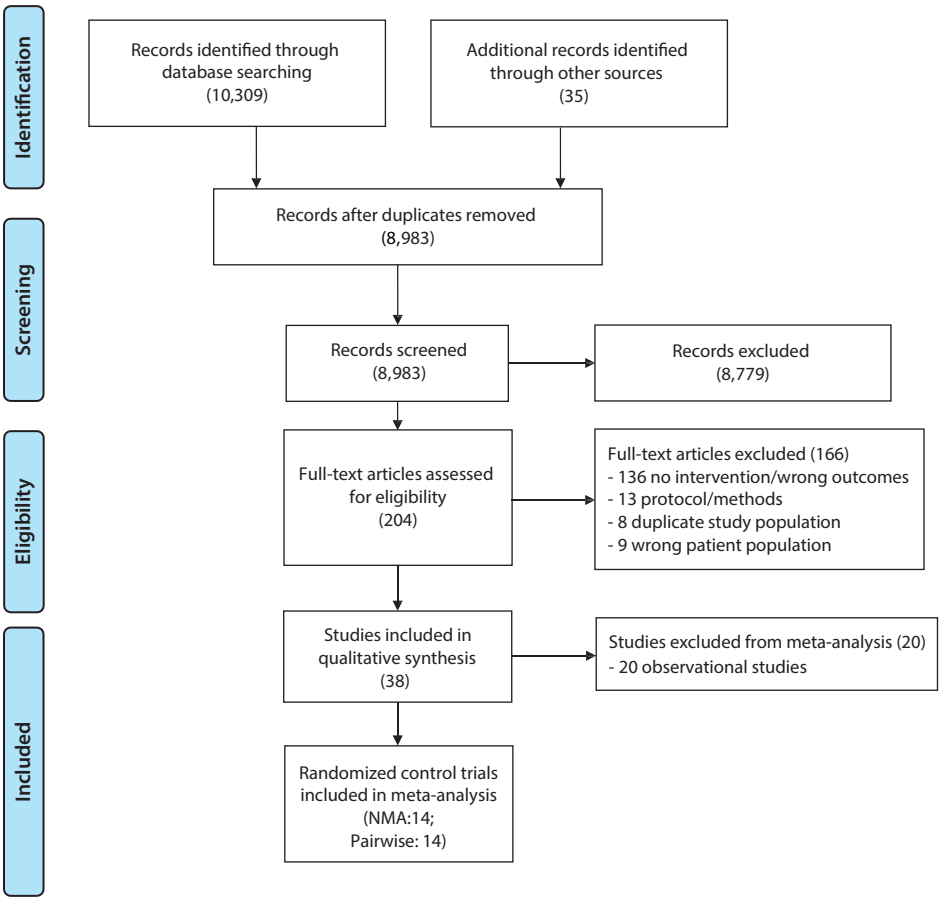
Features of Treatment Interventions and Controls

Interventions were diverse: CBT,[40,41,50,52,55,66,67,73] family therapy,[59,63,69] omega-3,[14,43,48] integrated psychological therapy (IPT),[42,46,68] CRT,[13,58] NMDAR modulators,[15,28] mood stabilizers,[47] and several types of antipsychotics such as risperidone or risperidone plus CBT,[53,61,62,71] aripiprazole,[56,78] olanzapine,[60] perospirone,[74] ziprasidone,[77] and varied/unspecified.[49,54,57,64,72,76]

Risk-of-Bias Assessment

Quality assessments are reported in Supplementary Figure 1. The majority of RCTs had a low risk of bias for

Figure 1. PRISMA Flow Diagram of Systematic Search and Included Studies



Abbreviations: NMA = network meta-analysis, PRISMA = Preferred Reporting Items for Systematic Reviews and Meta-Analyses.

random sequence generation (20 studies). RCTs had a higher risk of bias for attrition bias (7 studies) and blinding of participants and personnel (8 studies). Weighted risk-of-bias assessment in the network meta-analysis plot (Figure 2) for blinding of outcome assessments revealed that 4 edges had an unclear risk-of-bias, 3 edges had a low risk-of-bias, and 2 edges had a high risk-of-bias. Quality assessment of observational studies using ROBINS-I varied from serious to low (Supplementary Table 2), and the overall quality of the NMAs using GRADE varied between very low quality to moderate quality (Supplementary Table 3); however, the majority of the evidence from the NMAs was rated as having very low quality of evidence.

Network Pattern and Network Plot

The network formed 2 complex network plots at 6 and 12 months due to having a variety of interventions (Figure 2). In addition, the network plot had some sparse connections (eg, family therapy) with NBI and placebo being the most common comparators. The long-term network plot formed a simple network between CBT, NBI, and risperidone plus CBT (Supplementary Figure 5B).

Consistency and Publication Bias

Visual inspection of the comparison-adjusted funnel plots at 6- and 12-month follow-up for symmetry demonstrated the absence of small study effects with most observations falling on the null line (Supplementary Figure 2). Global tests of inconsistency found no statistically significant evidence of inconsistency in the NMAs. In addition, inconsistency plots formed 2 quadratic loops, which found no statistically significant evidence of inconsistency in the NMAs (Supplementary Figure 3).

Psychosocial Interventions

In the pairwise analyses, CBT interventions were not associated with a significant reduction in transition rates compared with controls at 6 months (RR = 0.66; 95% CI, 0.33–1.34; $I^2 = 19\%$; $P = .25$, 6 studies, N = 729; Supplementary Figure 7). However, CBT interventions were associated with a significant reduction in transition rates compared with controls at 12 and at 18 months (RR = 0.57; 95% CI, 0.35–0.93; $I^2 = 7\%$; $P = .02$, 6 studies, N = 729 vs RR = 0.54; 95% CI, 0.32–0.92; $I^2 = 0\%$; $P = .02$, 3 studies, N = 540). CBT trended toward statistical significance in reducing transition

Table 1. Details of the 38 Included Studies

Study Lead Author, y	Country	Study Design	Intervention	Control	Treatment Duration, wk	Study Centers, n	CHR Criterion	CHR Patients			Transition Results	Transition Measure	Included in Analysis
								N	Age, mean ± SD	Male, n (%)			
Cognitive-Behavioral Therapy													
Addington, 2011[40]	Canada	RCT	CBT	Supportive therapy	24	1	SIPS	51	CBT: 20.8 ± 4.5 Supportive: 21.1 ± 3.7	36 (70)	CBT: 0 Supportive: 3	SIPS	NMA, PW
Bechdolf, 2017[b,41]	Germany	RCT	CBT	Aripiprazole: 5–15 mg/d + CM/placebo + CM	52	9	SIPS, COGDIS	216	24.4 ± 5.1	143 (66)	NR	SIPS	Qualitative synthesis only
Fusar-Poli, 2015[50]	United Kingdom	Naturalistic	CBT	CBT + AP/CBT + AD/CBT + AP + AD	104	NR	CAARMS	258	22.9 ± 4.5	146 (57)	47	CAARMS	Qualitative synthesis only
Ising, 2016[52]	Netherlands	RCT	CBT + TAU	TAU	24	6	CAARMS	201	CBT: 22.7 ± 5.6 TAU: 22.6 ± 5.4	97 (49)	CBT: 12 TAU: 22	CAARMS	NMA, PW
Kim, 2011[55]	Korea	Open label	CBT	None	10	1	SIPS	22	19.4 ± 4.4	11 (50)	2	SIPS	Qualitative synthesis only
Morrison, 2004[67]	United Kingdom	RCT	CBT	Monitoring	26	NR	PANSS	58	22 ± 4.5	40 (69)	CBT: 7 Monitoring: 5	PANSS	NMA, PW
Morrison, 2012[66]	United Kingdom	RCT	CBT + monitoring	Monitoring	24	5	CAARMS	288	20.7 ± 4.3	180 (63)	CBT: 10 Monitoring: 13	CAARMS	NMA, PW
Stain, 2016[73]	Australia, New Zealand	RCT	CBT + TAU	TAU	24	2	CAARMS	57	CBT: 16.2 ± 2.7 TAU: 16.5 ± 3.2	23 (40)	CBT+TAU: 3 TAU: 0	CAARMS	NMA, PW
Family-Based Therapy													
McFarlane, 2015[59]	USA	RDD[b]	FACT	None	NR	6	SIPS	205	16.4 ± 3.3	116 (57)	FACT: 13	SIPS	Qualitative synthesis only
Miklowitz, 2014[63]	Canada, USA	RCT	FFT	Enhanced care	24	8	SIPS	129	17.4 ± 4.1	74 (57)	FFT: 1 Enhanced care: 5	SIPS	NMA
O'Brien, 2007[69]	USA	Open label	PMFG	None	38	1	SIPS	16	15.7 ± NR	8 (50)	PMFG: 3	SIPS	Qualitative synthesis only
Omega-3													
Amminger, 2010[43,45]	Austria	RCT	Omega-3 PUFA: 1.2 g/d	Placebo	12	1	APS	81	Omega: 16.8 ± 2.4 Placebo: 16.0 ± 1.7	27 (33)	Omega-3: 4 Placebo: 16	PANSS	NMA, PW
Cadenhead, 2017[48]	Canada, USA	RCT	Omega-3: 740 cmg EPA, 400 cmg DHA/d	Placebo	24	8	SIPS	127	18.8 ± NR	71 (56)	Omega-3: 4 Placebo: 3[c]	SIPS	NMA, PW
McGorry, 2017[14]	Multinational	RCT	Omega-3 PUFA: 1.4 g/d + CBCM	Placebo + CBCM	24	10	CAARMS	304	19.1 ± 4.6	139 (46)	Omega-3: 17 Placebo: 15[c]	CAARMS	NMA, PW
Cognitive Remediation													
Choi, 2016[13]	USA	RCT	CRT	Active control	8	2	SIPS	62	CRT: 18.2 ± 3.8 AC: 18.5 ± 3.7	30 (52)	CRT: 2 Control: 3[c]	SIPS	Qualitative synthesis only
Loewy, 2016[58]	USA	RCT	CRT	Computer games	8	1	SIPS	83	CRT: 17.8 ± 3.1 Control: 18.7 ± 4.6	42 (51)	Not enough power to present[c]	SIPS	Qualitative synthesis only

(continued)

Table 1 (continued).

Study Lead Author, y	Country	Study Design	Intervention	Control	Treatment Duration, wk	Study Centers, n	CHR Criterion	CHR Patients			Transition Results	Transition Measure	Included in Analysis
								N	Age, mean ± SD	Male, n (%)			
Integrated Psychological Therapy													
Albert, 2016[42]	Denmark	RCT	IPT	TAU	104	6	*ICD-10* schizotypal disorder	83	26.6 ± 4.4	38 (46)	IPT: 9 TAU: 10	SAPS, SCAN	PW
Bechdolf, 2012[46]	Germany	RCT	IPT	Supportive therapy	52	4	EIPS	128	IPT: 25.2 ± 5.4 Supportive: 26.8 ± 6.2	81 (63)	IPT: 4 Supportive: 13	PANSS, *DSM-IV*	NMA
Nordentoft, 2006[68]	Denmark	RCT	IPT	TAU	104	NR	*ICD-10* schizotypal disorder	79	24.9 ± 4.9	53 (67)	IPT: 9 TAU: 14	SAPS, SCAN	PW
NMDAR Modulators													
Kantrowitz, 2016[15]	USA	RCT	D-serine: 60 mg/kg	Placebo	16	4	SIPS	35	D-serine: 20 ± 4.9 Placebo: 19 ± 3.5	23 (65)	D-serine: 1 Placebo: 2	SIPS	PW
Woods, 2013[28]	USA	Open label	Glycine: 0.8 g/kg/d	None	8	1	SIPS	10	17.3 ± 3.3	7 (70)	Glycine: 0	SIPS	Qualitative synthesis only
Woods, 2013[28]	USA	RCT	Glycine: 0.8 g/kg/d	Placebo	12	1	SIPS	8	Glycine: 15.3 ± 0.5 Placebo: 16.5 ± 2.4	6 (75)	Glycine: 0 Placebo: 1	SIPS	PW
Antipsychotics													
Aripiprazole													
Kobayashi, 2009[56]	Japan	Open label	Aripiprazole: 7.1–10.7 mg/d	None	8	3	SIPS	36	23.4 ± 5.6	15 (42)	0	SIPS	Qualitative synthesis only
Woods, 2007[78]	USA	Open label	Aripiprazole: 5–30 mg/d	None	8	1	SIPS	15	17.1 ± 5.5	8 (53)	Aripiprazole: 0	SIPS	Qualitative synthesis only
Risperidone or Risperidone + CBT													
Kéri, 2006[53]	Hungary	Open label	Haloperidol or risperidone: 0.5–2 mg/d	Psychoeducation or supportive therapy	24	1	CAARMS	52	21.6 ± 3.4	32 (62)	3	CAARMS	Qualitative synthesis only
McGorry, 2002[62]	Australia	RCT	Risperidone: 1–2 mg/d + CBT	NBI	24	1	*DSM-IV*	59	20 ± 4.0	34 (58)	Risperidone: 6 NBI: 10	BPRS, CASH	NMA, PW
McGorry, 2013[61]	Australia	RCT	Risperidone: 0.5–2 mg/d + CBT or CBT + placebo	Supportive therapy + placebo or monitoring	52	1	SIPS	193	18.1 ± 3.0	81 (42)	Risperidone + CBT: 7 CBT + placebo: 7 Supportive therapy + CBT: 6 Monitoring: 5	CAARMS	NMA, PW
Rybakowski, 2003[71]	Poland	Naturalistic	Risperidone: 0.5–2 mg/d	None	varied	1	NR	8	27.1 ± 10.6	4 (50)	Risperidone: 0	Not specified	Qualitative synthesis only
Other Antipsychotics													
Cornblatt, 2007[49]	USA	Naturalistic	Second-generation AP: varied	AD: varied	24	2	SIPS	48	AP: 16.3 ± 2.6 AD: 15.7 ± 1.9	29 (60)	AP: 12 AD: 0	SIPS	Qualitative synthesis only
Kim, 2012[54]	Korea	Naturalistic	Pharmacotherapy	None	NR	1	CAARMS	78	21.3 ± 4.2	53 (68)	14	CAARMS	Qualitative synthesis only
Liu, 2010[57]	Taiwan	Naturalistic	AP: varied	None	36	1	CAARMS	11	18.7 ± NR	6 (55)	4	CAARMS	Qualitative synthesis only

(continued)

Table 1 (continued).

Study Lead Author, y	Country	Study Design	Intervention	Control	Treatment Duration, wk	Study Centers, n	CHR Criterion	CHR Patients			Transition Results	Transition Measure	Included in Analysis
								N	Age, mean ± SD	Male, n (%)			
McGlashan, 2006[60]	Canada, USA	RCT	Olanzapine: 5–15 mg/d	Placebo	52	4	SIPS	60	Olanzapine: 8.2 ± 5.5 Placebo: 17.2 ± 4.0	39 (65)	Olanzapine: 5 Placebo: 11	SIPS	NMA
Morita, 2014[64]	Japan	Naturalistic	Supportive therapy and/or psychotropic medication	None	52	1	SIPS	46	23.5 ± 6.6	13 (28)	3	SIPS	Qualitative synthesis only
Shim, 2008[72]	Korea	Open label	AP: varied	None	varied	1	CAARMS	27	21.5 ± 4.8	16 (59)	AP: 2	CAARMS	Qualitative synthesis only
Tsujino, 2013[74]	Japan	Open label	Perospirone: 4.0–10.2 mg/d	None	26	1	SIPS	11	26.7 ± 6.5	4 (36)	Perospirone: 0	SIPS	Qualitative synthesis only
Walker, 2009[76]	Canada, USA	Naturalistic	AD/AP: varied	No medication	NR	8	SIPS	191	18.6 ± 4.7	107 (56)	43	CAARMS	Qualitative synthesis only
Woods, 2017[77]	USA	RCT	Ziprasidone: 20–160 mg/d	Placebo	51	6	SIPS	50	22.3 ± NR	32 (64)	Ziprasidone: 1 Placebo: 2[c]	SIPS	NMA
Mood Stabilizers													
Berger, 2012[47]	Australia	Open label	Low-dose lithium: 450 mg/d	Monitoring	52	1	ARMS	103	Lithium: 20.1 ± 3.4 Monitoring: 17.8 ± 2.6	45 (32)	Lithium: 1 Monitoring: 5[c]	CAARMS	Qualitative synthesis only

[a]Not enough data presented.
[b]Risk-based allocation design.
[c]Transition data obtained from corresponding authors and reporting at last follow-up.

Abbreviations: AD = antidepressants; AP = antipsychotics; APS = attenuated psychosis syndrome; ARMS = at-risk mental state for psychosis; BPRS = Brief Psychiatric Rating Scale; CAARMS = comprehensive assessment of at-risk mental states; CASH = comprehensive assessment of symptoms and history; CBCM = cognitive-behavioral case management; CBT = cognitive -behavioral therapy; CHR = clinical high-risk; CM = clinical management; COGDIS = cognitive disturbances; CRT = cognitive remediation therapy; DHA = docosahexaenoic acid; *DSM-IV* = *Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition; EIPS = early intervention in psychosis service; EPA = eicosapentaenoic acid; FACT = family-aided assertive community treatment; *ICD-10* = *International Classification of Diseases, Tenth Revision*; IPT = integrated psychological therapy; NBI = needs-based intervention; NFI = needs-focused intervention; NMA = network meta-analysis; NMDAR = *N*-methyl-D-aspartate-receptor; NR = not reported; PANSS = Positive and Negative Syndrome Scale; PMFG = psychoeducational multifamily group; PUFA = polyunsaturated fatty acid; PW = pairwise; RCT = randomized controlled trial; RDD = regression discontinuity design; SAPS = Scale for the Assessment of Positive Symptoms; SCAN = Schedules for Clinical Assessment of Neuropsychiatry; SD = standard deviation; SIPS = Structured Interview of Psychosis-risk Syndromes; TAU = treatment as usual; USA = United States of America.

rates compared with controls at 24- to 48-month follow-up (RR = 0.69; 95% CI, 0.44–1.08; I^2 = 0%; P = .11, 3 studies, N = 549). In the 6- and 12-month NMAs, CBT interventions were not significantly more effective at reducing transition compared with any other intervention (Figure 3).

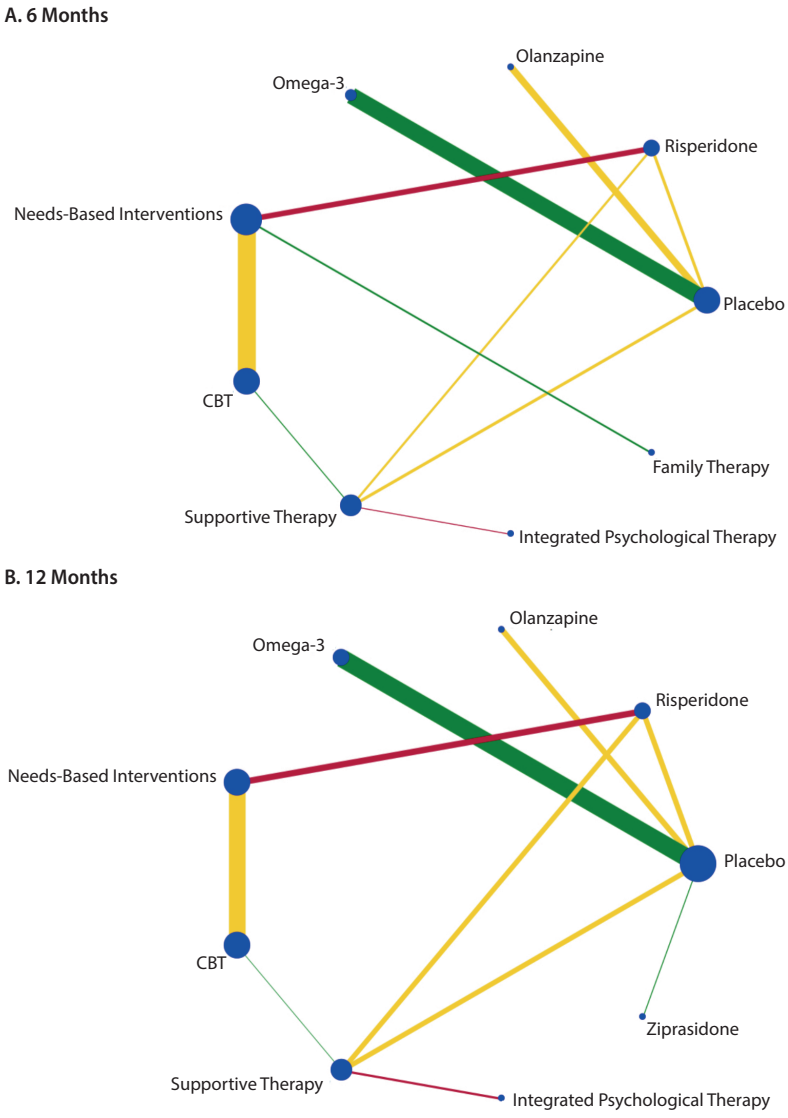
Family therapy could be analyzed only in the 6-month NMA due to having only 1 available RCT reporting 1 time point. In the NMA, family therapy was not significantly more effective at reducing transition compared with all other interventions.

IPT could be analyzed only in the NMAs (6- and 12-month) due to having only 1 available RCT. In the NMAs, IPT was not significantly more effective at reducing transition compared with any other intervention at 6- and 12-month follow-up (Figure 3). However, in the NMAs (6- and 12-month), there was a trend favoring IPT over the majority of interventions at reducing transition, albeit not statistically significant with all CIs crossing the null line. SUCRA plots of the absolute effects and rank test among the 10 treatments indicated that IPT ranked higher than the other 10 treatments, but this is in the context of no statistically supported efficacy compared with other interventions at both 6 and 12 months (see Supplementary Figure 4).

Antipsychotics

In the pairwise analyses, risperidone plus CBT interventions were associated with a significant reduction in transition rates at 6-month follow-up (RR = 0.34; 95% CI, 0.13–0.88; I^2 = 0%; P = .03, 2 studies, N = 146) but not at 12-month follow-up (RR = 0.72; 95% CI, 0.38–1.38; I^2 = 0%; P = .32, 2 studies, N = 146; Supplementary Figure 8). In the 6-month and 12-month NMAs, risperidone plus CBT interventions were not significantly more effective at reducing transition compared with any other intervention. Olanzapine could be analyzed only in the 6- and 12-month NMAs due to its having only 1 available study and was not significantly more effective at reducing transition compared with any other intervention. Similarly, ziprasidone could be analyzed only in the 12-month NMA due to its having only 1 available study and was not significantly

Figure 2. Six- and 12-Month Network Plots[a]



[a]Nodes are weighted according to the number of studies included in the respective interventions. Edges are weighted according to the number of studies including either that treatment or that comparison. Colored edges (green = low risk, yellow = unclear risk, red = high risk) according to risk-of-bias for blinding of outcome assessments, estimated as the level of bias in the majority of the trials and weighted according to the number of studies in each comparison.
Abbreviations: CBT = cognitive-behavioral therapy, PRISMA= Preferred Reporting Items for Systematic Reviews and Meta-Analyses.

more effective at reducing transition compared with any other intervention.

Omega-3

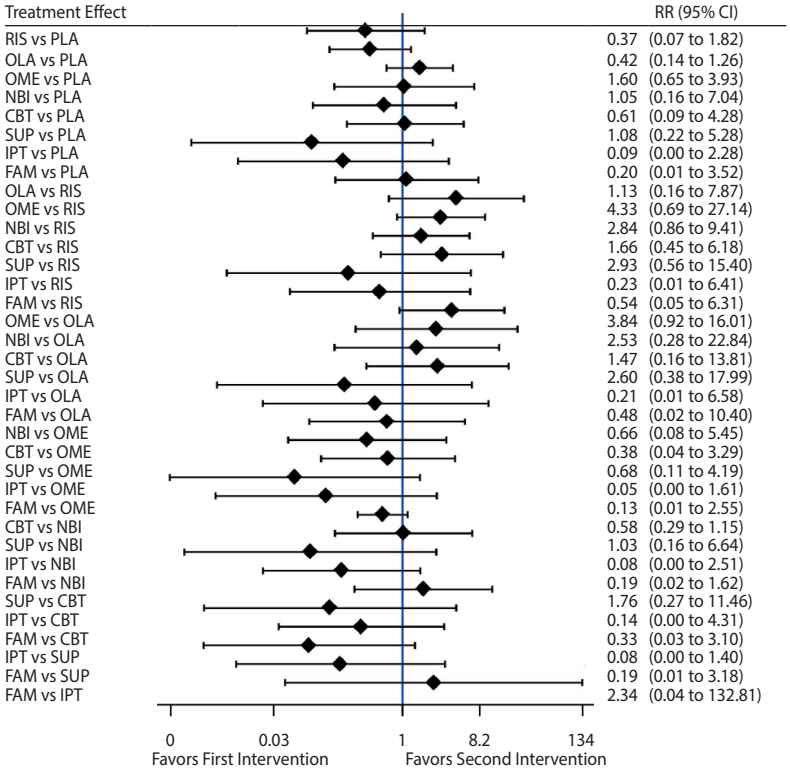
In the pairwise analyses, omega-3 interventions were not associated with a significant reduction in transition at 6-month, 12-month, or long-term follow-up compared with placebo (6-month: RR = 1.59; 95% CI, 0.68–3.76; $I^2 = 0\%$; $P = .29$, 2 studies, N = 431 vs 12-month: RR = 0.69; 95% CI, 0.21–2.27; $I^2 = 64\%$; $P = .54$, 3 studies, N = 512 vs long-term follow-up: RR = 0.51; 95% CI, 0.10–2.55; $I^2 = 70\%$; $P = .41$, 2 studies, N = 208; Supplementary Figure 9). In the 6-month and 12-month NMAs, omega-3 was not significantly more effective at reducing transition compared with any other intervention.

NMDAR Modulators

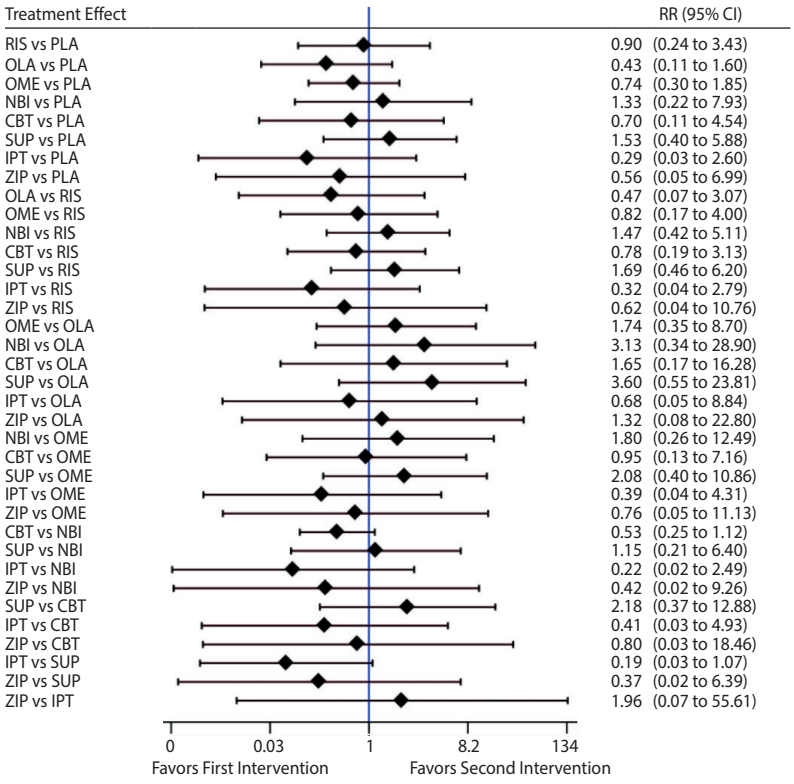
In the pairwise analyses, NMDAR modulator interventions were not associated with a significant reduction in transition compared with placebo (RR = 0.48; 95% CI, 0.08–2.98; $I^2 = 0\%$; $P = .43$, 2 studies, N = 52; Supplementary Figure 10) at 12- to 16-week follow-up. No NMDAR modulator studies were evaluated in the NMAs due to no comparable time-point (eg, 6 or 12 months).

Figure 3. Six- and 12-Month Forest Plots of the Transition Network Meta-Analysis[a]

A. 6 Months



B. 12 Months



[a]1 = null line.

Abbreviations: CBT = cognitive-behavioral therapy, FAM = family therapy (6-mo), IPT = integrated psychological therapy, NBI = needs-based interventions, OLA = olanzapine, OME = omega-3, PLA = placebo, RIS = risperidone, RR = risk ratio, SUP = supportive therapy, ZIP = ziprasidone (12-mo).

Cognitive Remediation Therapy

CRT was not evaluated in the pairwise meta-analyses due to having only 1 study. No CRT studies were evaluated in the NMA because it was not connected to any treatment in the network.

Integrated Treatment in Schizotypy

In the pairwise analyses, integrated treatments were not associated with a significant reduction in transition compared with standard care at long-term follow-up in studies that targeted schizotypal participants (RR = 0.74; 95% CI, 0.42–1.31; $I^2 = 14\%$; $P = .30$, 2 studies, N = 162; Supplementary Figure 11). Schizotypal studies were not assessed in the transition NMA because it would contravene the transitivity assumption.

Sensitivity Analyses

Sensitivity analyses were performed for both the 6- and 12-month NMAs by dropping studies that had a high risk of bias for blinding of assessments. The sensitively analyses confirmed that no interventions were significantly more effective at reducing transition compared with all other interventions in the network meta-analyses at any time point (Supplementary Figure 6).

DISCUSSION

In summary, this systematic review compared the effects of psychosocial interventions, antipsychotic medications, omega-3, and NMDAR modulators on transition to psychosis in CHR populations using both pairwise and network meta-analyses. First, pairwise meta-analyses revealed that CBT was associated with a significant reduction in transition compared with control treatments at 12- and 18-month follow-up, with a trend toward significance at long-term follow-up (24–48 months), whereas, risperidone plus CBT interventions were associated with a significant reduction in transition rates at 6-month follow-up. NMDAR modulators and omega-3 were not significantly better than placebo in pairwise analyses.

In the NMAs, there were no significant results with all CIs crossing the null line, meaning that no treatments significantly reduced transition relative to each other,

although there were some trends that may be of interest. First, there was a trend favoring IPT over the majority of interventions at both 6- and 12-month follow-ups. After performing sensitivity analyses, we noted a trend emerged favoring family therapy over the majority of interventions at 6 months and favoring CBT at 12 months, compared with all other treatments.

CBT demonstrated a statistically significant benefit over control treatments at reducing transition at 12- and 18-month follow-up. This finding is somewhat contrary to a previous meta-analysis[12] that reported that CBT reduced transition to psychosis at 6, 12, and 18–24 months. However, in the present review we did find a trend toward a significant reduction in transition at long-term follow-up. The discrepancy at 6 months in significance between reviews may be due to the presence of 2 additional CBT studies, both of which demonstrated no impact on transition compared with controls. In addition, the previous review included an IPT therapy at 6 months in its analysis, which may have biased results in favor of CBT.[46] Nevertheless, both this current review and the previous reviews[11,12] demonstrated a reduced risk for transition to psychosis for CHR participants that were randomized to CBT. Last, a trend emerged favoring CBT at reducing transition compared with all other therapies after removing studies that had a high risk of bias for blinding of outcomes at 12 months and at long-term follow-up. However, the results were not significant. CBT has the most available trials to date, and thus the results are more robust and generalizable compared with all other treatment strategies that have been tested in CHR samples.

In the NMAs, there was a trend favoring IPT over the majority of interventions at reducing transition compared with all other treatments before sensitivity analyses. Although this finding was not significant, it does merit some further discussion. As is the case with many treatment trials in CHR, there was only 1 RCT examining IPT. Consequently, the results of the NMAs should be interpreted with caution. This study was heavily weighted toward CBT (25 sessions) and included group skills training (15 sessions), cognitive remediation (12 sessions), and psychoeducational multifamily group (3 sessions). Unfortunately, due to study design, it was not possible to evaluate the different treatment strategies, making it difficult to ascertain which component(s) may have had an impact on transition. However, IPT interventions have been tested in patients with schizophrenia and have been shown to improve a variety of outcomes such as social cognition, neurocognition, psychosocial functioning, and negative symptoms compared with control treatments, as demonstrated in a recent meta-analysis.[81]

Finally, there was a trend favoring family therapy relative to other treatments at reducing transition in the NMA at 6 months after the sensitivity analysis was performed, albeit it was not significant. Unfortunately, there was only 1 RCT examining family therapy in CHR youth, and thus the results of the NMAs should be interpreted with caution until more RCTs investigating the impact of family therapy in CHR samples occur. However, 1 observational study[59] in CHR samples has examined the impact of family therapy on transition in a CHR samples, and it reported favorable results for reducing transition compared with those at "clinically low risk." In addition, family interventions in patients with schizophrenia are recommended by numerous international clinical guidelines and have a well-established influence at reducing psychotic symptoms.[82] Finally, a recent meta-analysis[83] established that family interventions decreased both relapse and readmission rates in early psychosis samples.

The strength of this review is that it included 38 unique studies examining 13 different treatment interventions with more than 3,400 CHR youth. We searched numerous databases, hand searched references to identify interventions, extracted data in duplicate, published our protocol a priori, and followed PRISMA and MOOSE guidelines, thus making this review the most comprehensive systematic review and largest meta-analysis of transition interventions in CHR to date.

However, there are important limitations to consider. First, the quality of evidence in this literature was deficient as conveyed by the high risk-of-bias for blinding of outcome assessments and may bias our findings. However, after performing sensitivity analyses by removing low-quality studies, results were minimally affected, with the exception of the removal of the 1 IPT study. Future studies should attempt to minimize risk-of-bias to strengthen the overall quality of the CHR treatment literature, which may aid future meta-analysis in the precision and quality of their conclusions. In addition, future studies may wish to undertake RCTs instead of observational studies as RCTs provide higher quality studies that can be incorporated into meta-analysis.

Second, we were unable to include all treatment strategies from the current systematic review in the NMAs, largely due to differences in when transition to psychosis rates were reported in individual treatments (eg, NMDAR modulators). Therefore, these analyses were restricted to treatments and studies reporting transition to psychosis at 6-month, 12-month, or long-term follow-up, which may have influenced our ability to detect a true difference between other treatment interventions. Moreover, the vast majority of evidence in the NMA was rated as having had a low quality as reported in GRADE, and thus the network results should be interpreted with caution. In addition, we were unable to include all treatment types in the traditional pairwise meta-analyses because some types of treatments had fewer than 2 RCTs (ie, family therapy, IPT, CRT). Due to the difference in studies included in both the pairwise meta-analyses and the NMAs, the results should be interpreted accordingly.

Third, we pooled a variety of treatments that used different criteria to define transition to a psychotic disorder, which may have important implications when interpreting the present results. The majority of studies utilized the SIPS scale for defining transition in CHR, which requires the occurrence of 1 fully psychotic symptom for at least an

hour per day for an average of 4 days per week over the past month or 1 brief fully psychotic symptom that is dangerous or disorganizing. The second most common scale was the CAARMS,[84] which differs in that the psychotic symptom has to have been present only for more than 1 week, and no criterion for dangerousness or disorganization is included. Interestingly, despite the differences in CHR scales utilized to determine transition, a meta-analysis[85] demonstrated that transition risk remains relatively similar at multiple time-points regardless of what instrument is used. Furthermore, a recent study[86] validated a conversion algorithm that demonstrated excellent diagnostic accuracy in determining conversion between the SIPS and the CAARMS.

Fourth, omega-3 pairwise meta-analyses at 12 months and long-term follow-up demonstrated significant amounts of heterogeneity, but in reviews comprising very few studies, such as in this review and meta-analyses, the I^2 may not be accurate.[87]

Fifth, treatments included in this review had inconsistent follow-up periods, which presented a limitation when examining transition to psychosis. Due to the difference in follow-up times reported in different study types, not all studies could be included in each analysis. For example, CRT studies often reported a 3-month follow-up period whereas antipsychotics studies reported 6- and 12-month periods, thereby excluding CRT studies from the NMAs.

Another limitation in the current meta-analyses was that fidelity to treatment and comorbid diagnoses were not explored because the number of studies was too limited to perform a meta-regression. These potential mediators and moderators may impact the final outcome of interest, ie, transition rates, and may account for some of the discrepancies in transition rates in the various studies.

The findings of the current systematic review lead to a few potential areas for future research. First, IPT demonstrated a trend of reducing transition relative to other treatments, and although not significant, merits further investigation, as IPT offers a package of interventions such as family education, CBT, social skills training, and CRT, and may be an effective early intervention for other symptoms such as attenuated psychotic and negative symptoms, mood, and poor social and role functioning. Alternatively, a modular-based treatment program similar to that used in the Recovery After an Initial Schizophrenia Episode (RAISE) Early Treatment Program[88,89] may be effective for those at CHR. In RAISE, through shared decision-making, participants were able to select from a range of programs that included medication management, family education, and individual resiliency training that included CBT and supported education and employment.

Next, more RCTs are needed with family therapy to support the results observed within this review. Such investigations may want to consider age of the young person, impact of expressed emotion[90] and implementation.[82] Moreover, family studies should investigate what specific components of the therapy are more effective at reducing transition, such as family involvement and communication training.

In conclusion, this systematic review and meta-analyses demonstrated a reduced risk for transition favoring CBT at 12 and 18 months. However, no interventions were significantly more effective at reducing transition compared with each other in the network meta-analysis. IPT and family therapy, although promising, require more clinical trials to determine a more precise and generalizable effect in CHR youth.

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Supplementary Material

Article Title: Interventions and Transition in Youth at Risk of Psychosis: A Systematic Review and Meta-Analyses

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6. Figure 2 — Network Comparison-Adjusted Funnel Plots
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Supplementary Search 1. Transition Search Strategies Examples

Database: Ovid MEDLINE(R)

1 exp psychotic disorders/ (47422)
2 deficit syndrome.ti,ab. (347)
3 exp schizophrenia/ (96189)
4 ((chronic$ or serious or persistent or severe$) adj (mental$ or psychological$) adj (disorder$ or ill$)).mp. (9524)
5 (delusion$ or hebephreni$ or psychosis or psychoses or psychotic$ or schizo$).mp. (208786)
6 or/1-5 (214816)
7 risk factors/ (683418)
8 symptom$.sh. or (prodrom$ or risk$).hw. (987343)
9 (blips or brief limited intermittent psychotic symptom$ or ((attenuat$ or early or pre?monitory) adj2 (sign$ or symptom$)) or pre?delusion$ or pre?hallucin$ or pre?psychos$ or pre?psychotic$ or pre?schizo$ or (pre adj (delusion$ or hallucin$ or psychos$ or psychotic$ or schizo$)) or prodrom$ or sub?clinical$ or sub?threshold$ or at risk$ or ((high$ or incipient or increas$) adj3 risk$)).ti,ab,kw. (796772)
10 or/8-9 (1523318)
11 (conversion$ or ((develop$ or progress$) adj2 (psychos$ or psychotic$ or schiz$)) or first episode$ or fullthreshold$ or full threshold$ or onset$ or progression or transition$ or transitory).ti,ab. (1272434)
12 10 and 11 (124494)
13 clinical high risk.ti,ab. (456)
14 ultra high risk.ti,ab. (700)
15 basic symptoms.ti,ab. (246)
16 attenuated psychosis syndrome.ti,ab. (60)
17 at risk mental state.ti,ab. (269)
18 ((at risk or ((high or increase$) adj2 risk) or blips or brief limited intermittent psychotic symptom$ or ((attenuat$ or early or premonitory) adj2 (sign$ or symptom$)) or prodrom$ or subclinical$ or sub$ clinical$ or subthreshold or sub$ threshold) and (psychos$ or psychotic$ or schiz$)).ti. or ((at risk or ((high or increase$) adj2 risk) or blips or brief limited intermittent psychotic symptom$ or ((attenuat$ or earlyor premonitory) adj2 (sign$ or symptom$)) or prodrom$ or subclinical$ or sub$ clinical$ or subthreshold or sub$ threshold) adj3 (psychos$ or psychotic$ or schiz$)).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms] (4992)
19 or/13-18 (5497)
20 (Experimental or interventional or experiment$ or multiple arm trial$ or clinical trial$ or double blind or randomization or random sample or placebo or RCT$ or randomized control trial or doubleblind$ or singleblind$ or tripleblind or block design$ or cluster randomized trial$ or two-arm trial$).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol

supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms] (3078666)
21 (treatment or case-crossover or ecological or naturalistic or case-control or non-randomized controlled trial or controlled before after study or interrupted time series study or historically controlled study or cohort study or cross-sectional study or quasi-design or quasi-experimental designs or quasi or factorial designs or time series designs or uncontrolled before after studies or open label or openlabel).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms] (4552593)
22 20 and 21 (849367)
23 6 and (7 or 12 or 19) and 22 (579)

Database: Embase
1 exp psychotic disorders/ (262725)
2 deficit syndrome.ti,ab. (482)
3 exp schizophrenia/ (173439)
4 ((chronic$ or serious or persistent or severe$) adj (mental$ or psychological$) adj (disorder$ or ill$)).mp. (11717)
5 (delusion$ or hebephreni$ or psychosis or psychoses or psychotic$ or schizo$).mp. (289781)
6 or/1-5 (317140)
7 risk factors/ (429596)
8 symptom$.sh. or (prodrom$ or risk$).hw. (2677408)
9 (blips or brief limited intermittent psychotic symptom$ or ((attenuat$ or early or pre?monitory) adj2 (sign$ or symptom$)) or pre?delusion$ or pre?hallucin$ or pre?psychos$ or pre?psychotic$ or pre?schizo$ or (pre adj (delusion$ or hallucin$ or psychos$ or psychotic$ or schizo$)) or prodrom$ or sub?clinical$ or sub?threshold$ or at risk$ or ((high$ or incipient or increas$) adj3 risk$)).ti,ab,kw. (1123392)
10 or/8-9 (3005604)
11 (conversion$ or ((develop$ or progress$) adj2 (psychos$ or psychotic$ or schiz$)) or first episode$ or fullthreshold$ or full threshold$ or onset$ or progression or transition$ or transitory).ti,ab. (1610550)
12 10 and 11 (277648)
13 clinical high risk.ti,ab. (854)
14 ultra high risk.ti,ab. (1436)
15 basic symptoms.ti,ab. (466)
16 attenuated psychosis syndrome.ti,ab. (99)
17 at risk mental state.ti,ab. (627)
18 ((at risk or ((high or increase$) adj2 risk) or blips or brief limited intermittent psychotic symptom$ or ((attenuat$ or early or premonitory) adj2 (sign$ or symptom$)) or prodrom$ or subclinical$ or sub$ clinical$ or subthreshold or sub$ threshold) and (psychos$ or psychotic$ or schiz$)).ti. or ((at risk or ((high or increase$) adj2 risk) or blips

or brief limited intermittent psychotic symptom$ or ((attenuat$ or earlyor premonitory) adj2 (sign$ or symptom$)) or prodrom$ or subclinical$ or sub$ clinical$ or subthreshold or sub$ threshold) adj3 (psychos$ or psychotic$ or schiz$)).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading] (8067)
19 or/13-18 (9060)
20 (Experimental or interventional or experiment$ or multiple arm trial$ or clinical trial$ or double blind or randomization or random sample or placebo or RCT$ or randomized control trial or doubleblind$ or singleblind$ or tripleblind or block design$ or cluster randomized trial$ or two-arm trial$).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading] (5780300)
21 (treatment or case-crossover or ecological or naturalistic or case-control or non-randomized controlled trial or controlled before after study or interrupted time series study or historically controlled study or cohort study or cross-sectional study or quasi-design or quasi-experimental designs or quasi or factorial designs or time series designs or uncontrolled before after studies or open label or openlabel).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading] (6190361)
22 20 and 21 (1682879)
23 6 and (7 or 12 or 19) and 22 (2189)

Database: EMB Reviews
1 psychotic disorders.mp. (114)
2 deficit syndrome.mp. (0)
3 schizophrenia.mp. (402)
4 ((chronic* or serious or persistent or severe*) adj (mental* or psychological*) adj (disorder* or ill*)).mp. (70)
5 (delusion* or hebephreni* or psychosis or psychoses or psychotic* or schizo*).mp. (554)
6 1 or 2 or 3 or 4 or 5 (598)
7 risk factors.mp. (2761)
8 (symptom* or (prodrom* or risk*)).mp. (12470)
9 (blips or brief limited intermittent psychotic symptom* or ((attenuat* or early or pre?monitory) adj2 (sign* or symptom*)) or pre?delusion* or pre?hallucin* or pre?psychos* or pre?psychotic* or pre?schizo* or (pre adj (delusion* or hallucin* or psychos* or psychotic* or schizo*)) or prodrom* or sub?clinical* or sub?threshold* or at risk* or ((high* or incipient or increas*) adj3 risk*)).mp. (10903)
10 or/8-9 (12479)
11 (conversion* or ((develop* or progress*) adj2 (psychos* or psychotic* or schiz*)) or first episode* or fullthreshold* or full threshold* or onset* or progression or transition* or transitory).mp. (1768)

12 10 and 11 (1167)
13 clinical high risk.mp. (0)
14 ultra high risk.mp. (3)
15 basic symptoms.mp. (1)
16 attenuated psychosis syndrome.mp. (0)
17 at risk mental state.mp. (0)
18 ((at risk or ((high or increase*) adj2 risk) or blips or brief limited intermittent psychotic symptom* or ((attenuat* or early or premonitory) adj2 (sign* or symptom*)) or prodrom* or subclinical* or sub* clinical* or subthreshold or sub* threshold) and (psychos* or psychotic* or schiz*)).ti. or ((at risk or ((high or increase*) adj2 risk) or blips or brief limited intermittent psychotic symptom* or ((attenuat* or earlyor premonitory) adj2 (sign* or symptom*)) or prodrom* or subclinical* or sub* clinical* or subthreshold or sub* threshold) adj3 (psychos* or psychotic* or schiz*)).mp. (33)
19 or/13-18 (33)
20 (Experimental or interventional or experiment* or multiple arm trial* or clinical trial* or double blind or randomization or random sample or placebo or RCT* or randomized control trial or doubleblind* or singleblind* or tripleblind or block design* or cluster randomized trial* or two-arm trial*).mp. [mp=title, full text, keywords] (11903)
21 (treatment or case-crossover or ecological or naturalistic or case-control or non-randomized controlled trial or controlled before after study or interrupted time series study or historically controlled study or cohort study or cross-sectional study or quasi-design or quasi-experimental designs or quasi or factorial designs or time series designs or uncontrolled before after studies or open label or openlabel).mp. [mp=title, full text, keywords] (17024)
22 20 and 21 (9620)
23 6 and (7 or 12 or 19) and 22 (62)

Database: PsychINFO
1 exp psychosis/ (103886)
2 deficit syndrome.ti,ab. (289)
3 exp schizophrenia/ (81402)
4 ((chronic* or serious or persistent or severe*) adj (mental* or psychological*) adj (disorder* or ill*)).mp. (13290)
5 (delusion* or hebephreni* or psychosis or psychoses or psychotic* or schizo*).mp. (174521)
6 or/1-5 (184458)
7 risk factors/ (64138)
8 symptom*.sh. or (prodrom* or risk*).hw. (180124)
9 (blips or brief limited intermittent psychotic symptom* or ((attenuat* or early or pre?monitory) adj2 (sign* or symptom*)) or pre?delusion* or pre?hallucin* or pre?psychos* or pre?psychotic* or pre?schizo* or (pre adj (delusion* or hallucin* or

psychos* or psychotic* or schizo*)) or prodrom* or sub?clinical* or sub?threshold* or at risk* or ((high* or incipient or increas*) adj3 risk*)).ti,ab,kw. (137684)
10 or/8-9 (264103)
11 (conversion* or ((develop* or progress*) adj2 (psychos* or psychotic* or schiz*)) or first episode* or fullthreshold* or full threshold* or onset* or progression or transition* or transitory).ti,ab. (182961)
12 10 and 11 (24934)
13 clinical high risk.ti,ab. (380)
14 ultra high risk.ti,ab. (608)
15 basic symptoms.ti,ab. (211)
16 attenuated psychosis syndrome.ti,ab. (68)
17 ((at risk or ((high or increase*) adj2 risk) or blips or brief limited intermittent psychotic symptom* or ((attenuat* or early or premonitory) adj2 (sign* or symptom*)) or prodrom* or subclinical* or sub* clinical* or subthreshold or sub* threshold) and (psychos* or psychotic* or schiz*)).ti. or ((at risk or ((high or increase*) adj2 risk) or blips or brief limited intermittent psychotic symptom* or ((attenuat* or earlyor premonitory) adj2 (sign* or symptom*)) or prodrom* or subclinical* or sub* clinical* or subthreshold or sub* threshold) adj3 (psychos* or psychotic* or schiz*)).mp. [mp=title, abstract, heading word, table of contents, key concepts, original title, tests & measures] (4874)
18 exp at risk populations/ (34452)
19 or/13-18 (37901)
20 (Experimental or interventional or experiment* or multiple arm trial* or clinical trial* or double blind or randomization or random sample or placebo or RCT* or randomized control trial or doubleblind* or singleblind* or tripleblind or block design* or cluster randomized trial* or two-arm trial*).mp. [mp=title, abstract, heading word, table of contents, key concepts, original title, tests & measures] (521516)
21 (treatment or case-crossover or ecological or naturalistic or case-control or non-randomized controlled trial or controlled before after study or interrupted time series study or historically controlled study or cohort study or cross-sectional study or quasi-design or quasi-experimental designs or quasi or factorial designs or time series designs or uncontrolled before after studies or open label or openlabel).mp. [mp=title, abstract, heading word, table of contents, key concepts, original title, tests & measures] (658596)
22 20 or 21 (1083370)
23 6 and (7 or 12 or 19) and 22 (4695)

Database: CINAHL

S1 (MH "Psychotic Disorders+") OR "psychotic disorders" OR (MH "Schizophrenia+") OR "schizophrenia"

S2 "ultra high risk" OR "clinical high risk" OR "basic symptoms" OR "attenuated psychosis syndrome" or "conversion" OR "transition" or (MH "Risk Factors") OR "risk factors"

S3 "experimental" OR "interventional" OR "experiment*" OR "multiple arm trial*" OR "clinical trial*" OR "double blind" OR "randomization" OR "random sample" OR "placebo" OR "RCT*" OR "randomized control trial" OR "doubleblind*" OR "singleblind*" OR "tripleblind" OR "block design*" OR "cluster randomized trial*" OR "two-arm trial*"

S4 S1 AND S2 AND S3

Supplementary Table 1. PRISMA Checklists for Both Transition Pairwise and Network Meta-Analysis

A. Transition Pairwise Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1*
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	3
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	3-4
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	4
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	5
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	3
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	3, Supplementary Material 2
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	3
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	5-6
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	5-6

Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	6
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	6-7
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I_2) for each meta-analysis.	6-8

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	6-8
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	8
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	9
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	9-10
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	10
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	10-15, Supplementary 5
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	10-15
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	10, Figure 2
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	NA
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	15-16
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	16-18
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	18-19

FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	19

*** page numbers correspond to the original word document and do not reflect the page numbers in the published manuscript for both A and B.**

B. Transition NMA Checklist. Checklist of Items to Include When Reporting A Systematic Review Involving a Network Meta-analysis

Section/Topic	Item #	Checklist Item	Reported on Page #
TITLE			
Title	1	Identify the report as a systematic review *incorporating a network meta-analysis (or related form of meta-analysis).*	***1***
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: **Background:** main objectives **Methods:** data sources; study eligibility criteria, participants, and interventions; study appraisal; and *synthesis methods, such as network meta-analysis.* **Results:** number of studies and participants identified; summary estimates with corresponding confidence/credible intervals; *treatment rankings may also be discussed. Authors may choose to summarize pairwise comparisons against a chosen treatment included in their analyses for brevity.* **Discussion/Conclusions:** limitations; conclusions and implications of findings. **Other:** primary source of funding; systematic review registration number with registry name.	2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known, *including mention of why a network meta-analysis has been conducted.*	***3***
Objectives	4	Provide an explicit statement of questions being addressed, with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	***3-4***
METHODS			
Protocol and registration	5	Indicate whether a review protocol exists and if and where it can be accessed (e.g., Web address); and, if available, provide registration information, including registration number.	4

Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale. *Clearly describe eligible treatments included in the treatment network, and note whether any have been clustered or merged into the same node (with justification).*	***5***
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	***3***
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	***3, SM 2***
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	3
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	***5-6***
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	***5-6***
Geometry of the network	**S1**	Describe methods used to explore the geometry of the treatment network under study and potential biases related to it. This should include how the evidence base has been graphically summarized for presentation, and what characteristics were compiled and used to describe the evidence base to readers.	***6-7, 10, Figure 3***
Risk of bias within individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	***6, Figure 3***
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means). *Also describe the use of additional summary measures assessed, such as treatment rankings and surface under the cumulative ranking curve (SUCRA) values, as well as modified approaches used to present summary findings from meta-analyses.*	***6-8***
Planned methods of analysis	14	Describe the methods of handling data and combining results of studies for each network meta-analysis. This should include, but not be limited to: • *Handling of multi-arm trials;* • *Selection of variance structure;* • *Selection of prior distributions in Bayesian analyses; and* • *Assessment of model fit.*	***6-8***
Assessment of Inconsistency	**S2**	Describe the statistical methods used to evaluate the agreement of direct and indirect evidence in the treatment network(s) studied. Describe efforts taken to address its presence when found.	***6-8***
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	***6-8***
Additional analyses	16	Describe methods of additional analyses if done, indicating which were pre-specified. This may include, but not be limited to, the following: • Sensitivity or subgroup analyses; • Meta-regression analyses; • *Alternative formulations of the treatment network; and* • *Use of alternative prior distributions for Bayesian analyses (if applicable).*	***6-8***

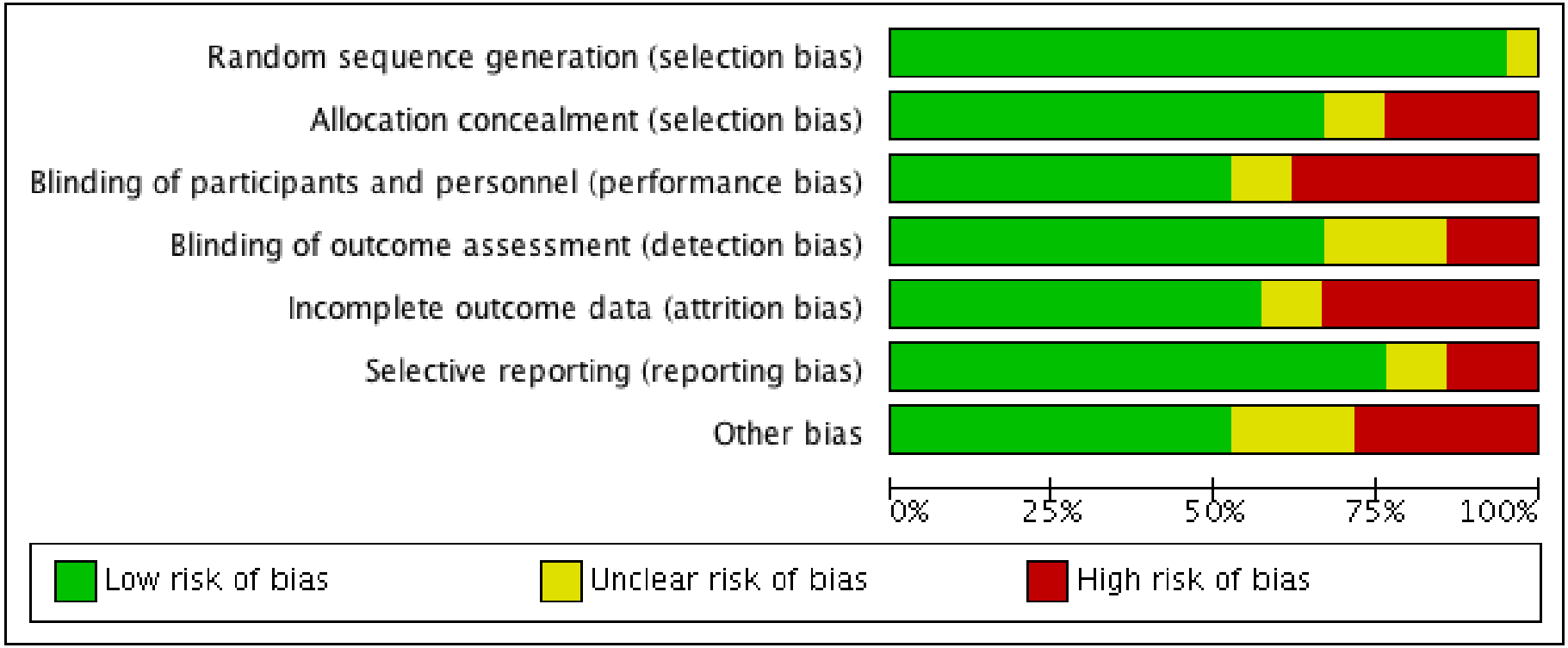
RESULTS†			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	***9***
Presentation of network structure	**S3**	Provide a network graph of the included studies to enable visualization of the geometry of the treatment network.	***10-11, Figure 3***
Summary of network geometry	**S4**	Provide a brief overview of characteristics of the treatment network. This may include commentary on the abundance of trials and randomized patients for the different interventions and pairwise comparisons in the network, gaps of evidence in the treatment network, and potential biases reflected by the network structure.	***10-11***
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	***Table 1***
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment.	***10, Figure 2, Figure 3***
Results of individual studies	20	*For all outcomes considered (benefits or harms), present, for each study: 1) simple summary data for each intervention group, and 2) effect estimates and confidence intervals. Modified approaches may be needed to deal with information from larger networks.*	***11-15***
Synthesis of results	21	*Present results of each meta-analysis done, including confidence/credible intervals. In larger networks, authors may focus on comparisons versus a particular comparator (e.g. placebo or standard care), with full findings presented in an appendix. League tables and forest plots may be considered to summarize pairwise comparisons. If additional summary measures were explored (such as treatment rankings), these should also be presented.*	***11-15, Figure 4***
Exploration for inconsistency	**S5**	Describe results from investigations of inconsistency. This may include such information as measures of model fit to compare consistency and inconsistency models, *P* values from statistical tests, or summary of inconsistency estimates from different parts of the treatment network.	***11***
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies for the evidence base being studied.	***10, Figure 2, Figure 3***
Results of additional analyses	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression analyses, *alternative network geometries studied, alternative choice of prior distributions for Bayesian analyses,* and so forth).	***NA***
DISCUSSION			
Summary of evidence	24	Summarize the main findings, including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy-makers).	***15-16***

Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review level (e.g., incomplete retrieval of identified research, reporting bias). *Comment on the validity of the assumptions, such as transitivity and consistency. Comment on any concerns regarding network geometry (e.g., avoidance of certain comparisons).*	***17-18***
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	***18-19***
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review. This should also include information regarding whether funding has been received from manufacturers of treatments in the network and/or whether some of the authors are content experts with professional conflicts of interest that could affect use of treatments in the network.	***19***

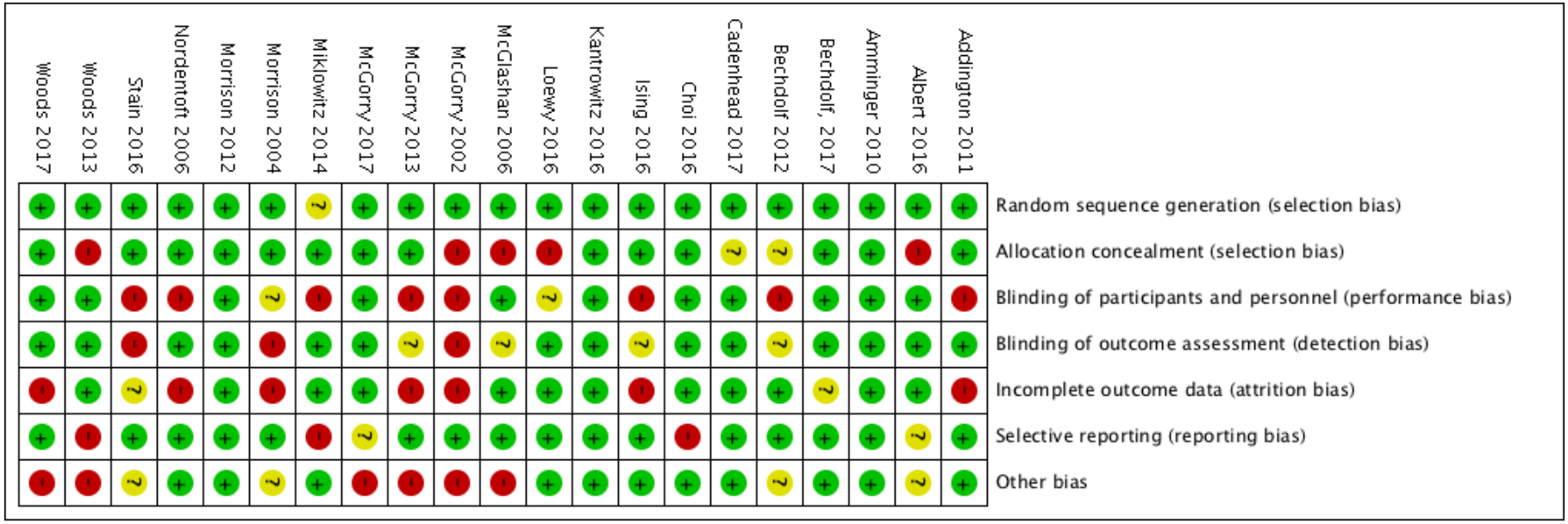
PICOS = population, intervention, comparators, outcomes, study design.

Supplementary Figure 1. Risk-of-Bias Assessments

A. Cochrane Risk-of-Bias Assessment for RCTs: Graph



B. Cochrane Risk-of-Bias Assessment for RCTs: Summary



A. Risk of bias graph for RCTs: review authors' judgements about each risk of bias item presented as percentages across all included studies.

B. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.

Supplementary Table 2. ROBINS-I Risk-of-Bias Assessment for Nonrandomized Studies

Author, Year	Biases							
	Confounding	Selection of participants	Classification of interventions	Deviations from intended interventions	Missing data	Measurement of outcomes	Selection of reported result	Overall Bias
Berger, 2012	Low	NI	Low	NI	NI	NI	NI	NI
Cornblatt, 2007	Moderate	Serious	Moderate	Low	Moderate	Moderate	Low	Serious
Fusar-Poli, 2015	Serious	Moderate	Serious	Low	NI	Low	Low	Serious
Kerri, 2006	Low	Low	Low	Moderate	Low	Moderate	Low	Moderate
Kim, 2011	Moderate	Low	Low	Low	Low	Moderate	Low	Moderate
Kim, 2012	Serious	Low	Serious	Moderate	Low	Moderate	Moderate	Serious
Kobayashi, 2009	Low	Low	Moderate	Low	Low	Moderate	Low	Moderate
Liu, 2010	Low	Low	Low	NI	Low	Moderate	Moderate	Moderate
McFarlane, 2015	Low	Serious	Low	Moderate	Moderate	Low	Moderate	Serious
Morita, 2014	Moderate	Low	Moderate	Serious	Moderate	Moderate	Moderate	Serious
O'Brien, 2007	Low	Low	Low	Low	Moderate	Moderate	Moderate	Moderate
Rybakowski, 2003	Low	Low	Low	Low	Low	Moderate	Low	Moderate
Shim, 2008	Moderate	Low	Moderate	Serious	Moderate	NI	Low	Serious
Tsujino, 2013	Low	Low	Moderate	NI	Low	Moderate	Low	Moderate
Walker, 2009	Serious	Serious	Moderate	Moderate	NI	Moderate	Serious	Serious
Woods, 2007	Low	Low	Low	Low	Low	Moderate	Low	Moderate
Woods, 2013	Low	Low	Low	Low	Low	Moderate	Moderate	Moderate

Supplementary Table 3. GRADE Risk-of-Bias Assessment

Intervention	Comparator	# of trials for direct comparison	NMA RR (95% CI)	Risk of bias ‡	Inconsistency §	Indirectness ¥	Imprecision χ	Publication bias Ψ	Overall Quality
6-months									
RIS	PLA	0	0.36 (0.07, 2.00)			*	**		Very low
OLA	PLA	1	0.42 (0.12, 1.49)	*			*		Low
OME	PLA	3	0.74 (0.30, 1.85)				*		Moderate
NBI	PLA	0	1.33 (0.22, 7.93)			*	**		Very low
CBT	PLA	1	0.62 (0.08, 5.08)	*			**		Very low
SUP	PLA	0	1.10 (0.20, 6.01)			*	**		Very low
IPT	PLA	0	0.09 (0.00, 2.60)			*	**		Very low
FAM	PLA	0	0.19 (0.01, 3.88)			*	**		Very low
OLA	RIS	0	1.15 (0.14, 9.65)			*	**		Very low
OME	RIS	0	4.43 (0.60, 32.98)			*	**		Very low
NBI	RIS	1	2.70 (0.71, 10.20)	*			**		Very low
CBT	RIS	1	1.71 (0.39, 7.38)	*			**		Very low
SUP	RIS	1	3.03 (0.53, 17.29)	*			**		Very low
IPT	RIS	0	0.24 (0.01, 7.33)			*	**		Very low
FAM	RIS	0	0.52 (0.04, 6.92)			*	**		Very low
OME	OLA	0	3.87 (0.74, 20.16)			*	**		Very low
NBI	OLA	0	2.36 (0.21, 26.39)			*	**		Very low
CBT	OLA	0	1.49 (0.13, 17.42)			*	**		Very low
SUP	OLA	0	2.64 (0.32, 22.08)			*	**		Very low
IPT	OLA	0	0.21 (0.01, 7.88)			*	**		Very low
FAM	OLA	0	0.45 (0.02, 12.06)			*	**		Very low
NBI	OME	0	0.61 (0.06, 6.16)			*	**		Very low
CBT	OME	1	0.38 (0.04, 4.07)				**		Low
SUP	OME	0	0.68 (0.09, 5.02)			*	**		Very low
IPT	OME	0	0.05 (0.00, 1.89)			*	**		Very low
FAM	OME	0	0.12 (0.00, 2.89)			*	**		Very low
CBT	NBI	4	0.63 (0.30, 1.34)	*			*		Low
SUP	NBI	0	1.12 (0.16, 8.04)			*	**		Very low
IPT	NBI	0	0.09 (0.00, 3.06)			*	**		Very low
FAM	NBI	1	0.19 (0.02, 1.78)	*			*		Low
SUP	CBT	1	1.78 (0.24, 12.88)				**		Low
IPT	CBT	0	0.14 (0.00, 4.88)			*	**		Very low
FAM	CBT	0	0.30 (0.03, 3.19)			*	**		Very low
IPT	SUP	1	0.08 (0.00, 1.50)	*			*		Low
FAM	SUP	0	0.17 (0.01, 3.34)			*	**		Very low

FAM	IPT	0	2.14 (0.03, 140.72)			*	**		Very low
12-month									
RIS	PLA	0	0.90 (0.24, 3.43)			*	**		Very low
OLA	PLA	1	0.43 (0.11, 1.60)	*			*		Low
OME	PLA	3	0.74 (0.30, 1.85)				*		Moderate
NBI	PLA	0	1.33 (0.22, 7.93)			*	**		Very low
CBT	PLA	1	0.70 (0.11, 4.54)	*			**		Very low
SUP	PLA	0	1.53 (0.40, 5.88)			*	**		Very low
IPT	PLA	0	0.29 (0.03, 2.60)			*	**		Very low
ZIP	PLA	1	0.56 (0.05, 6.99)			*	**		Very low
OLA	RIS	0	0.47 (0.07, 3.07)			*	**		Very low
OME	RIS	0	0.82 (0.17, 4.00)			*	**		Very low
NBI	RIS	1	1.47 (0.42, 5.11)	*			**		Very low
CBT	RIS	1	0.78 (0.19, 3.13)	*			**		Very low
SUP	RIS	1	1.69 (0.46, 6.20)	*			**		Very low
IPT	RIS	0	0.32 (0.04, 2.79)			*	**		Very low
ZIP	RIS	0	0.62 (0.04, 10.76)			*	**		Very low
OME	OLA	0	1.74 (0.35, 8.70)			*	**		Very low
NBI	OLA	0	3.13 (0.34, 28.90)			*	**		Very low
CBT	OLA	0	1.65 (0.17, 16.28)			*	**		Very low
SUP	OLA	0	3.60 (0.55, 23.81)			*	**		Very low
IPT	OLA	0	0.68 (0.05, 8.84)			*	**		Very low
ZIP	OLA	0	1.32 (0.08, 22.80)			*	**		Very low
NBI	OME	0	1.80 (0.26, 12.49)			*	**		Very low
CBT	OME	1	0.95 (0.13, 7.16)				**		Low
SUP	OME	0	2.08 (0.40, 10.86)			*	**		Very low
IPT	OME	0	0.39 (0.04, 4.31)			*	**		Very low
ZIP	OME	0	0.76 (0.05, 11.13)			*	**		Very low
CBT	NBI	4	0.53 (0.25, 1.12)	*			*		Low
SUP	NBI	0	1.15 (0.21, 6.40)			*	**		Very low
IPT	NBI	0	0.22 (0.02, 2.49)			*	**		Very low
ZIP	NBI	0	0.42 (0.02, 9.26)				**		Low
SUP	CBT	1	2.18 (0.37, 12.88)				**		Low
IPT	CBT	0	0.41 (0.03, 4.93)			*	**		Very low
ZIP	CBT	0	0.80 (0.03, 18.46)			*	**		Very low
IPT	SUP	1	0.19 (0.03, 1.07)	*			*		Low
ZIP	SUP	0	0.37 (0.02, 6.39)			*	**		Very low
ZIP	IPT	0	1.96 (0.07, 55.61)			*	**		Very low
Long-term									
NBI	RIS	1	1.33 (0.68, 2.59)	*			**		Very low
CBT	RIS	1	0.87 (0.38, 1.99)	*			*		Low
CBT	NBI	0	0.65 (0.40, 1.08)			*	**		Very low

Abbreviations: PLA= Placebo; RIS= Risperidone; OLA= Olanzapine; OME= Omega-3; NBI= Needs-based interventions; CBT= Cognitive behavioral therapy; SUP= Supportive therapy; IPI= Integrated psychological interventions; FAM= Family therapy (6-months); ZIP= Ziprasidone (12-months)

‡ Risk-of-bias assessment based on rating from the Cochrane Risk-of-bias tool assessments.

§ Inconsistency was only assessed in intervention comparisons with >1 study.

¥ Indirectness was based on if there was an actual study with that intervention comparison. All comparisons were considered direct as all of this research was performed within the last 20 years and was restricted to CHR study populations.

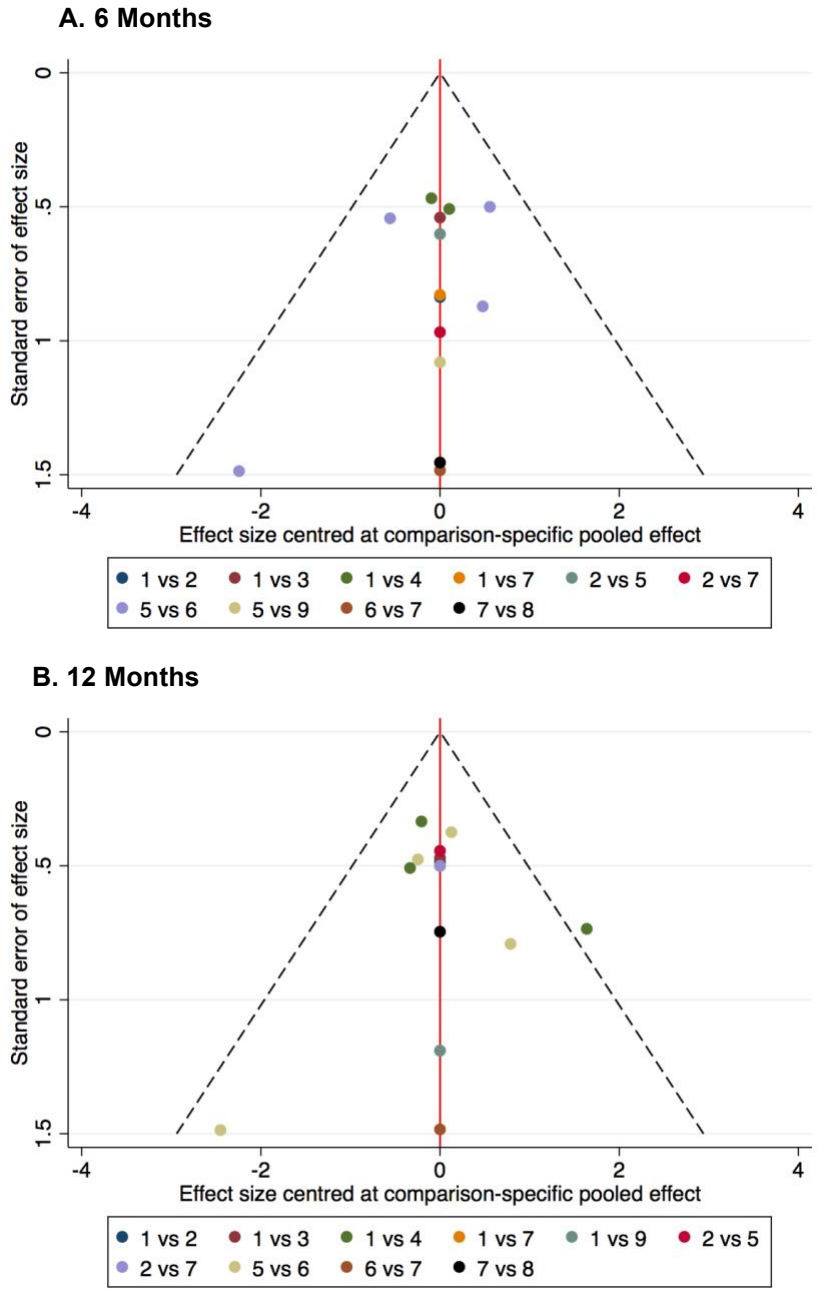
χ Imprecision was observed in all estimates, both direct and indirect for 6-, 12- months and long-term networks and therefore all estimates were downgraded by one point.

Ψ Publication bias was assessed based on the funnel plots. Since a comprehensive systematic literature review was concerned, publication bias is less of a concern.

* Downgraded by one point.

** Downgraded by two points.

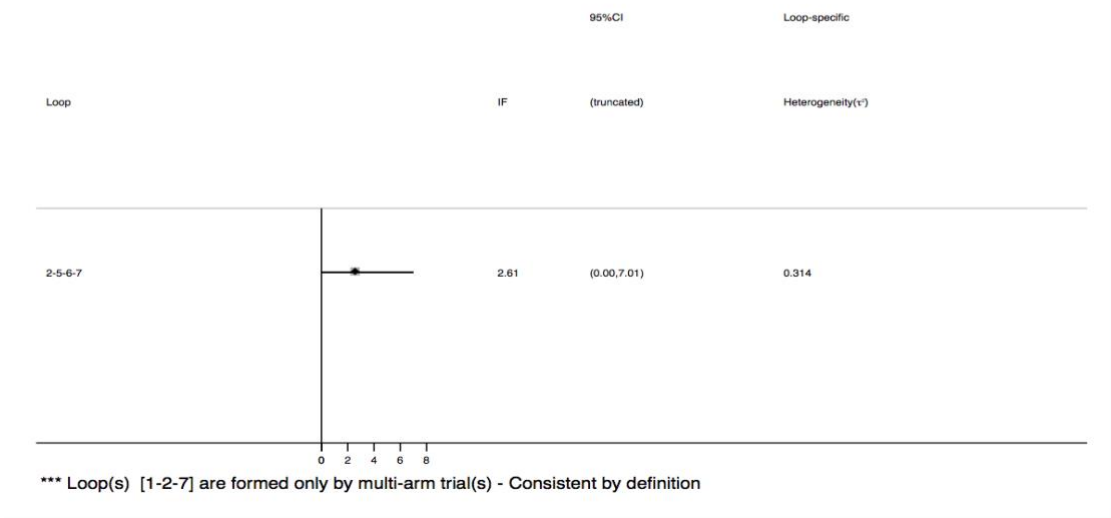
Supplementary Figure 2. Network Comparison-Adjusted Funnel Plots



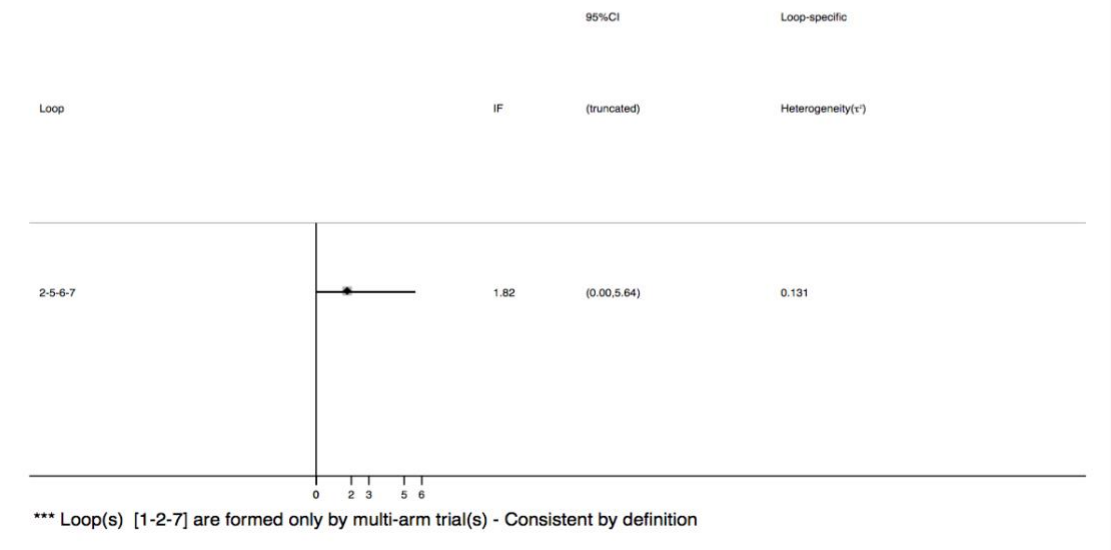
Comparison-adjusted funnel plot for the transition network at 6- and 12-months. Zero represents the null hypothesis that the study-specific effect sizes do not differ from the respective comparison-specific pooled effect estimates. Different colours correspond to different comparisons. Abbreviations: 1= Placebo; 2= Risperidone; 3= Olanzapine; 4= Omega-3; 5= Needs-based interventions; 6= Cognitive behavioral therapy; 7= Supportive therapy; 8= Integrated psychological therapy; 9= Family therapy (6-months); 9= Ziprasidone (12-months)

Supplementary Figure 3. Inconsistency Plot

A. 6 Months



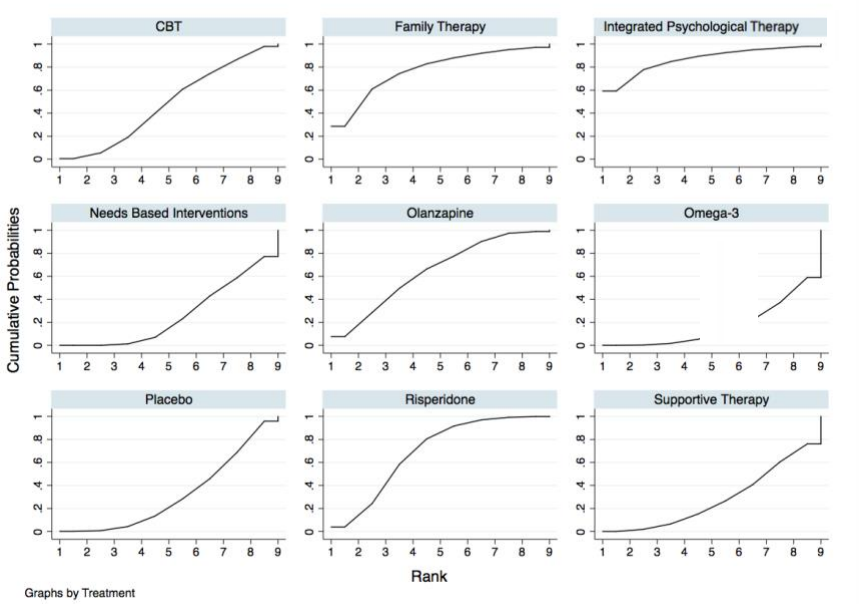
B. 12 Months



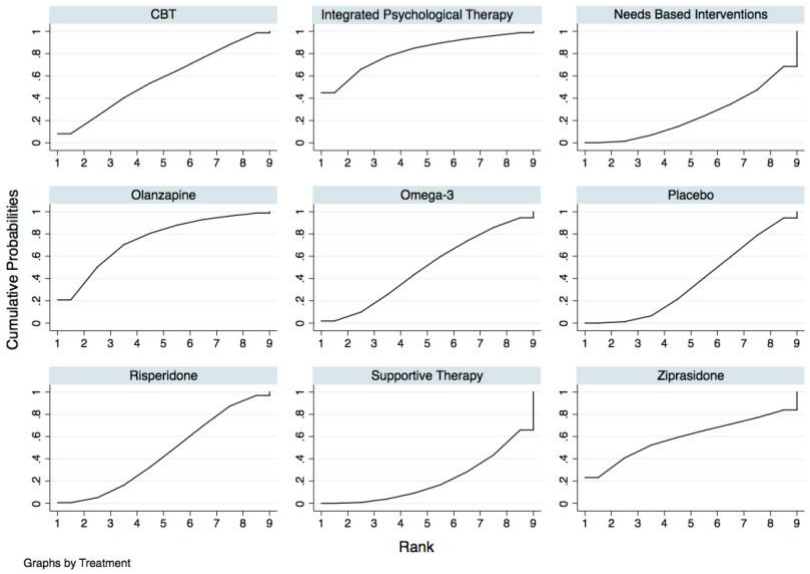
Inconsistency plot produced of one quadratic loop for both 6- and 12-months. Abbreviations: 01= Placebo; 02= Risperidone; 05= Needs-based interventions; 6= Cognitive behavioral therapy; 7= Supportive therapy

Supplementary Figure 4. Surface Under the Cumulative Ranking Curve (SUCRA)

A. 6 Months



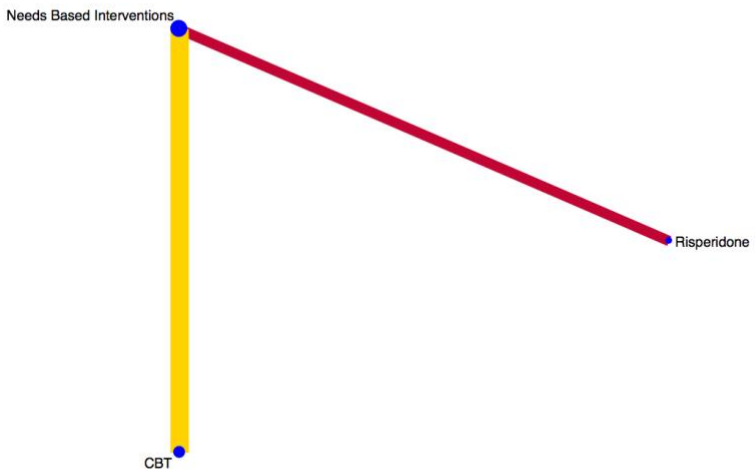
B. 12 Months



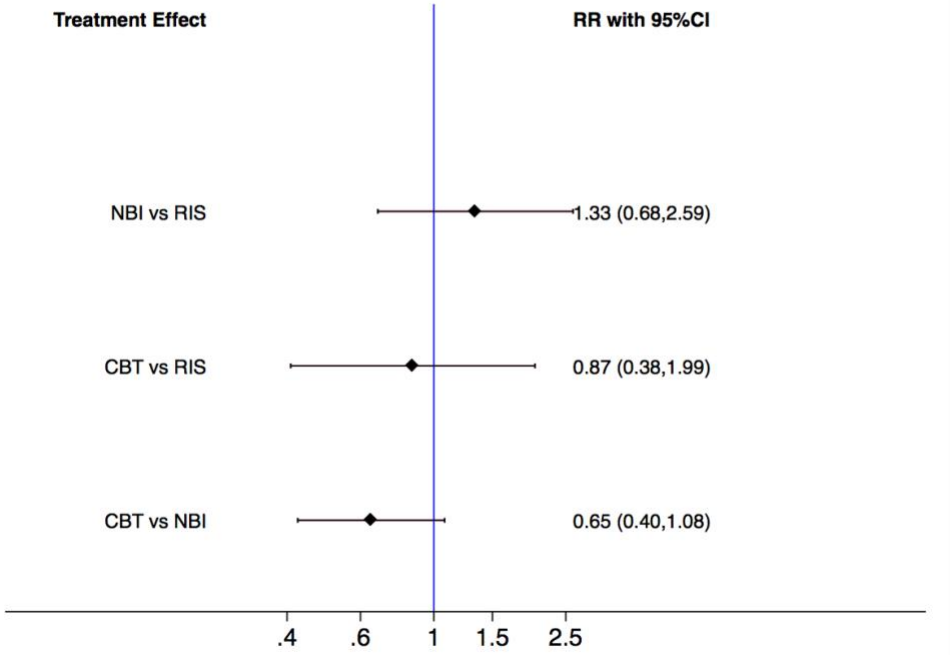
Plots of the surface under the cumulative ranking curves for all treatments in the transition network at 6- and 12-months. Black solid lines correspond to the unadjusted model. Abbreviations: CBT= Cognitive behavioral therapy

Supplementary Figure 5. Long-Term Follow-up Network

A. Long-Term Network Plot



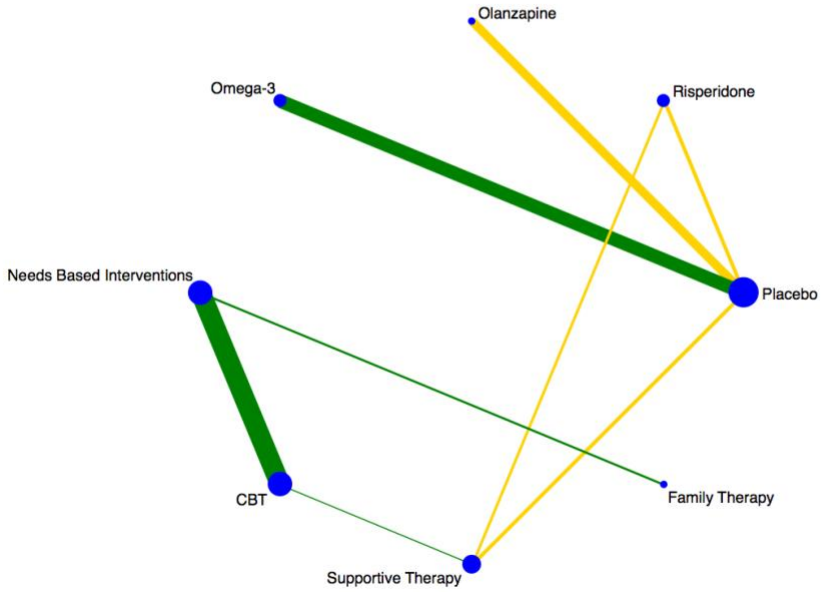
B. Long-Term Network Forest Plot



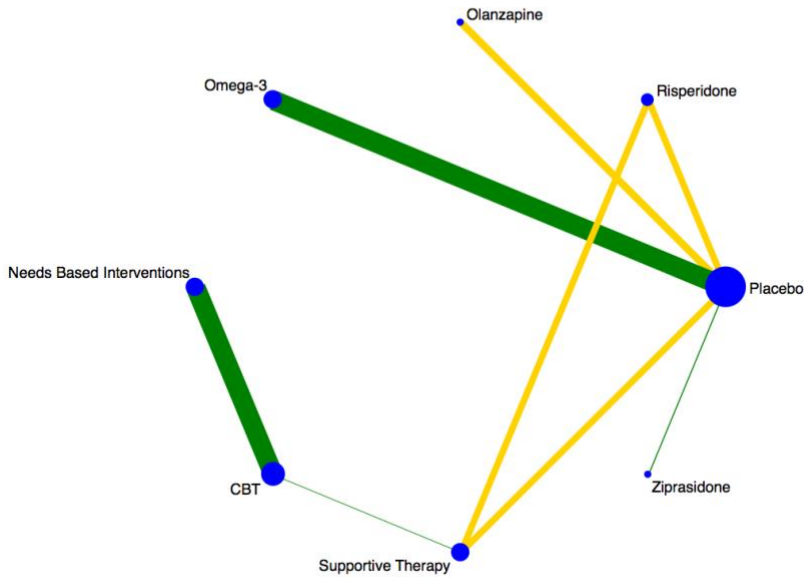
Abbreviations: CBT= Cognitive behavioral therapy; NBI= Needs-based interventions; RIS= Risperidone

Supplementary Figure 6. Sensitivity Analyses

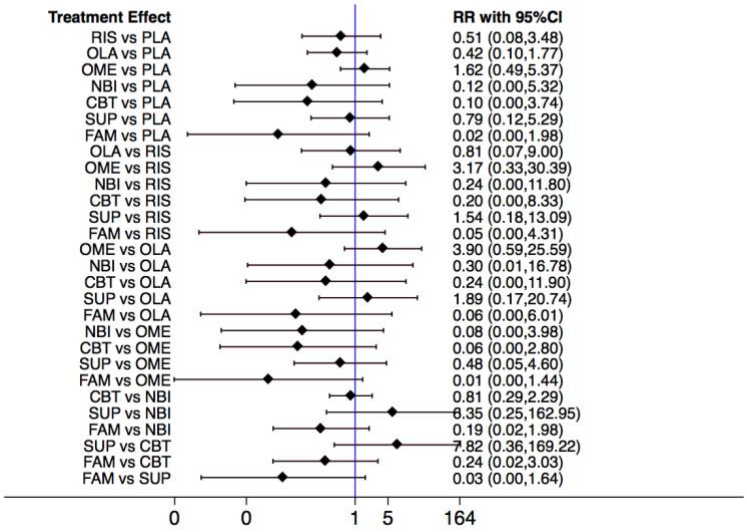
A. 6 Months



B. 12 Months

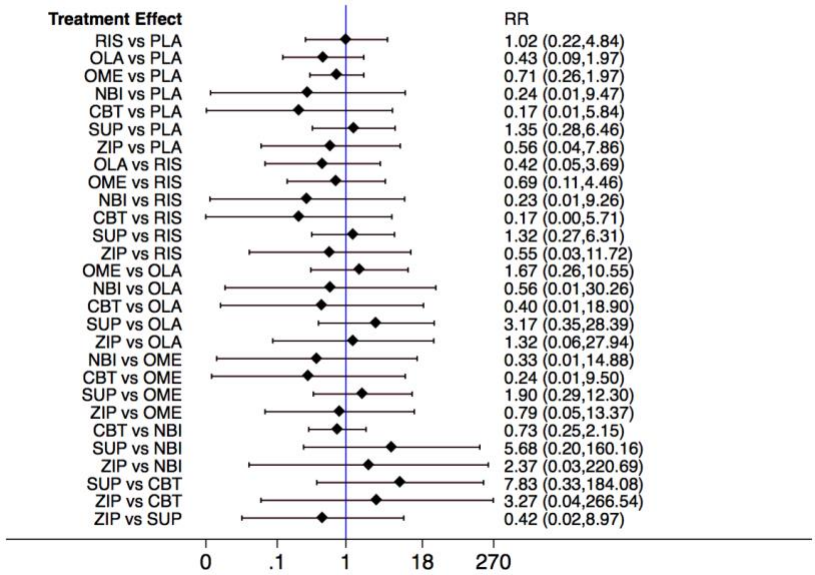


C. Sensitivity Analyses Forest Plot 6-Months



Favors First Intervention **Favors Second Intervention**

D. Sensitivity Analyses Forest Plot 12-Months



Favors First Intervention **Favors Second Intervention**

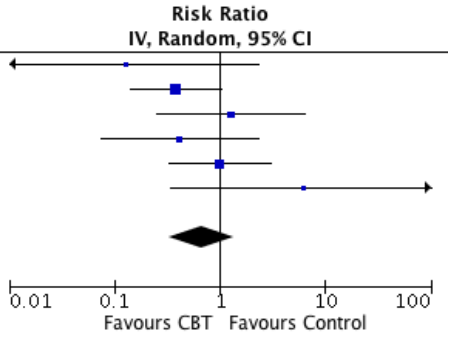
Sensitivity analysis of 6- and 12-month forest plots of the transition network meta-analysis (1=null line). Abbreviations: PLA = Placebo; RIS = Risperidone; OLA = Olanzapine; OME = Omega-3; NBI = Needs Based Interventions; CBT = Cognitive Behavioral Therapy; SUP= Supportive-Therapy; IPI = Integrated Psychological Interventions; FAM = Family-Therapy (6-months); ZIP = Ziprasidone (12-months)

Supplementary Figure 7. Pairwise Forest Plots CBT

A. 6 Months

Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Risk Ratio IV, Random, 95% CI
Addington 2011	0	27	3	24	5.4%	0.13 [0.01, 2.35]
Ising 2016	5	97	14	104	32.3%	0.38 [0.14, 1.02]
McGorry 2013z	4	44	2	28	15.3%	1.27 [0.25, 6.50]
Morrison 2004	2	37	3	23	14.1%	0.41 [0.07, 2.30]
Morrison 2012	6	144	6	144	27.6%	1.00 [0.33, 3.03]
Stain 2016	3	30	0	27	5.4%	6.32 [0.34, 117.09]
Total (95% CI)		**379**		**350**	**100.0%**	**0.66 [0.33, 1.34]**
Total events	20		28			

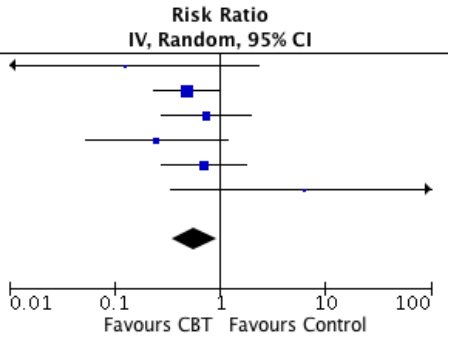
Heterogeneity: $Tau^2 = 0.14$; $Chi^2 = 6.15$, df = 5 (P = 0.29); $I^2 = 19\%$
Test for overall effect: Z = 1.15 (P = 0.25)



B. 12 Months

Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Risk Ratio IV, Random, 95% CI
Addington 2011	0	27	3	24	2.8%	0.13 [0.01, 2.35]
Ising 2016	9	97	20	104	37.4%	0.48 [0.23, 1.01]
McGorry 2013z	7	44	6	28	22.7%	0.74 [0.28, 1.98]
Morrison 2004	2	37	5	23	9.7%	0.25 [0.05, 1.18]
Morrison 2012	7	144	10	144	24.6%	0.70 [0.27, 1.79]
Stain 2016	3	30	0	27	2.8%	6.32 [0.34, 117.09]
Total (95% CI)		**379**		**350**	**100.0%**	**0.57 [0.35, 0.93]**
Total events	28		44			

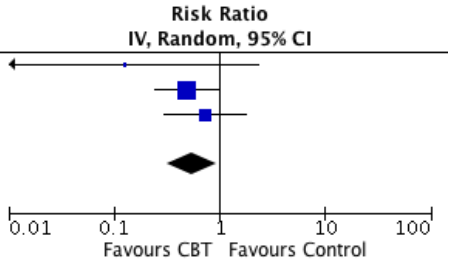
Heterogeneity: $Tau^2 = 0.03$; $Chi^2 = 5.38$, df = 5 (P = 0.37); $I^2 = 7\%$
Test for overall effect: Z = 2.25 (P = 0.02)



C. 18 Months

Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Risk Ratio IV, Random, 95% CI
Addington 2011	0	27	3	24	3.4%	0.13 [0.01, 2.35]
Ising 2016	10	97	22	104	59.6%	0.49 [0.24, 0.98]
Morrison 2012	8	144	11	144	37.0%	0.73 [0.30, 1.76]
Total (95% CI)		**268**		**272**	**100.0%**	**0.54 [0.32, 0.92]**
Total events	18		36			

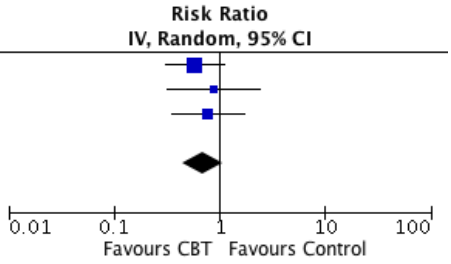
Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 1.46$, df = 2 (P = 0.48); $I^2 = 0\%$
Test for overall effect: Z = 2.25 (P = 0.02)



D. Long-Term (24 to 48 Months)

Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Risk Ratio IV, Random, 95% CI
Ising 2016	12	97	22	104	48.4%	0.58 [0.31, 1.12]
Morrison 2004	7	37	5	23	19.3%	0.87 [0.31, 2.42]
Morrison 2012	10	144	13	144	32.3%	0.77 [0.35, 1.70]
Total (95% CI)		**278**		**271**	**100.0%**	**0.69 [0.44, 1.08]**
Total events	29		40			

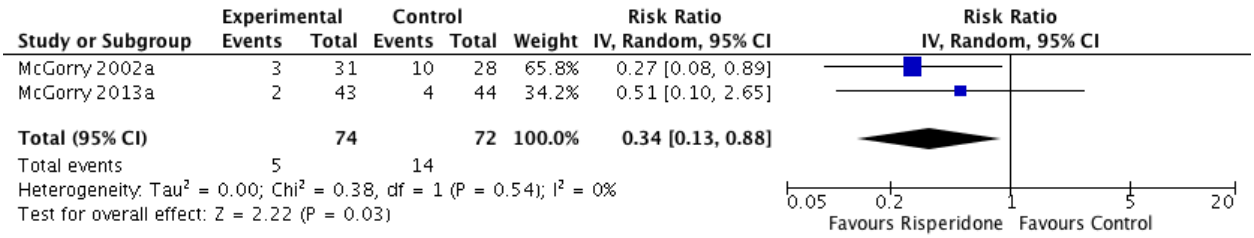
Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 0.52$, df = 2 (P = 0.77); $I^2 = 0\%$
Test for overall effect: Z = 1.62 (P = 0.11)



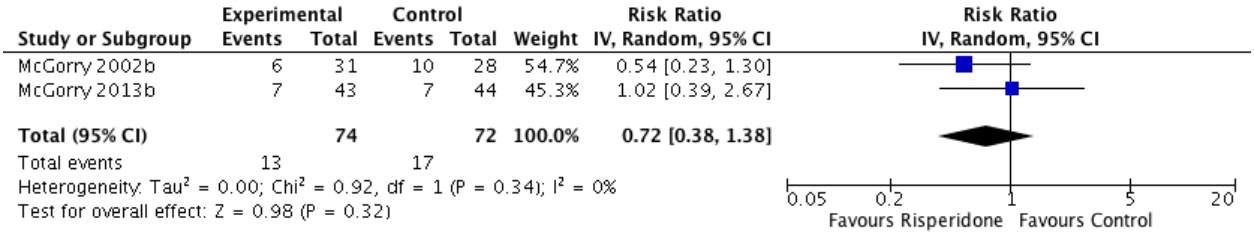
NOTES: Ising 2016 – randomized numbers reported in original van der Gaag et al., 2012 paper used for each time-point; z = CBT + placebo versus supportive + placebo; Morrison 2004 utilizing PANSS transition criteria & Morrison 2004 long-term follow-up as reported in Morrison et al., 2007 paper utilizing PANSS transition criteria.

Supplementary Figure 8. Pairwise Forest Plots Risperidone + CBT

A. 6 Months



B. 12 Months



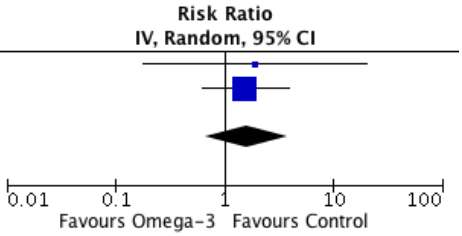
Risperidone + CBT versus controls impact on transition in CHR.

Supplementary Figure 9. Pairwise Forest Plots Omega-3

A. 6 Months

Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Risk Ratio IV, Random, 95% CI
Cadenhead 2017	2	65	1	62	13.1%	1.91 [0.18, 20.51]
McGorry 2016	11	153	7	151	86.9%	1.55 [0.62, 3.89]
Total (95% CI)		**218**		**213**	**100.0%**	**1.59 [0.68, 3.76]**
Total events	13		8			

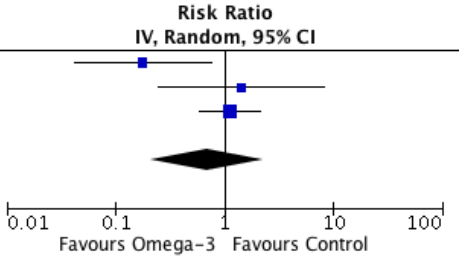
Heterogeneity: Tau² = 0.00; Chi² = 0.03, df = 1 (P = 0.87); I² = 0%
Test for overall effect: Z = 1.06 (P = 0.29)



B. 12 Months

Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Risk Ratio IV, Random, 95% CI
Amminger 2010	2	41	11	40	29.9%	0.18 [0.04, 0.75]
Cadenhead 2017	3	65	2	62	24.7%	1.43 [0.25, 8.28]
McGorry 2016	17	153	15	151	45.4%	1.12 [0.58, 2.16]
Total (95% CI)		**259**		**253**	**100.0%**	**0.69 [0.21, 2.27]**
Total events	22		28			

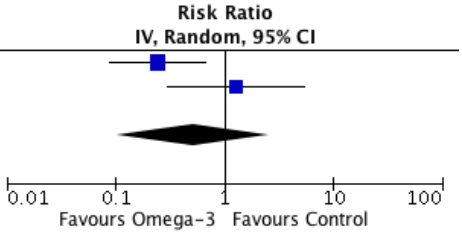
Heterogeneity: Tau² = 0.71; Chi² = 5.54, df = 2 (P = 0.06); I² = 64%
Test for overall effect: Z = 0.62 (P = 0.54)



C. Long-Term (post one-year)

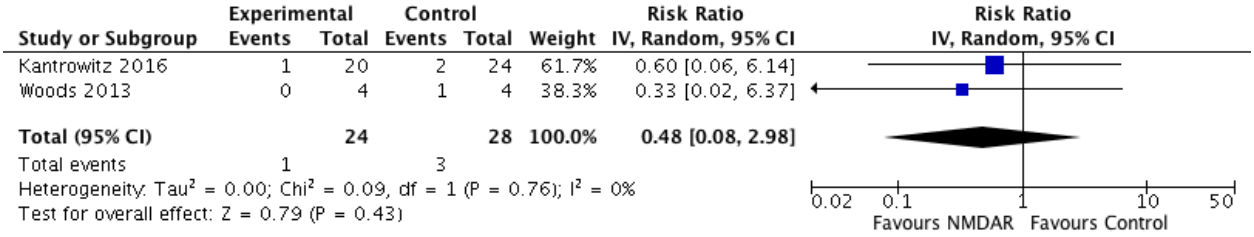
Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Risk Ratio IV, Random, 95% CI
Amminger 2010	4	41	16	40	55.3%	0.24 [0.09, 0.67]
Cadenhead 2017	4	65	3	62	44.7%	1.27 [0.30, 5.45]
Total (95% CI)		**106**		**102**	**100.0%**	**0.51 [0.10, 2.55]**
Total events	8		19			

Heterogeneity: Tau² = 0.96; Chi² = 3.35, df = 1 (P = 0.07); I² = 70%
Test for overall effect: Z = 0.82 (P = 0.41)



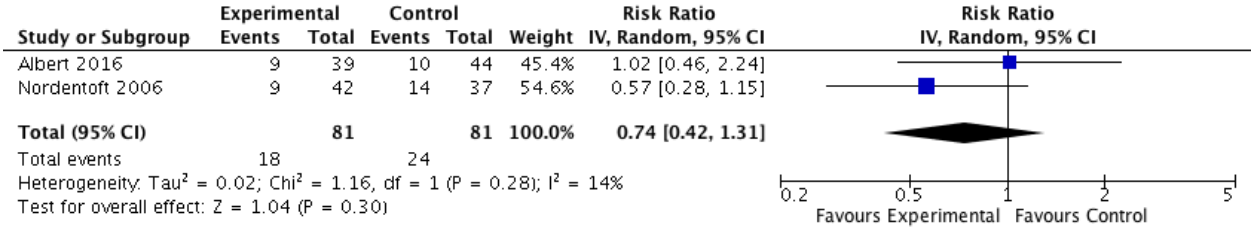
Notes: Amminger 2010 long-term outcome from Amminger et al., 2014

Supplementary Figure 10. Pairwise Forest Plots NMDAR Modulators



NMDAR impact on transition in CHR at 12- to 16-week follow-up. Kantrowitz 2016 includes 1 participant who transitioned at week 16.

Supplementary Figure 11. Pairwise Forest Plots Integrated Treatment (Schizotypal)



Note: Integrated treatment impact on transition in schizotypal participants at long-term follow-up using allocation n values for both experimental and control groups in both studies.