**Web appendices: Supplementary material**

*Appendix 1: Search Strategy For All Databases*

1.1 At risk terms

1.11 Embase, Medline, PreMEDLINE, PsycINFO – OVID SP

1. delusional disorder/ or "explode schizophrenia"/ or (psychosis$ or psychotic$).hw.
2. 1 use emez
3. exp psychotic disorders/ or "schizophrenia and disorders with psychotic features"/ or exp schizophrenia/ or schizophrenia, childhood/
4. 3 use mesz, prem
5. exp psychosis/ or schizoaffective disorder/ or thought disturbances/
6. 5 use psyh
7. (delusional disorder$ or 1ttenuate1c$ or psychosis or psychoses or psychotic$ or schizo$).ti,ab.
8. ((chronic$ or serious or persistent or severe$) adj (mental$ or psychological$) adj (disorder$ or ill$)).mp.
9. or/2,4,6-8
10. high risk patient/ or high risk population/ or ultra high risk criterion/ or ultra high risk population/
11. 10 use emez
12. *risk factors/
13. 12 use mesz, prem
14. at risk populations/
15. 14 use psyh
16. or/11,13,15
17. (symptom$ or symptomology).sh. or (prodrom$ or risk$).hw.
18. (blips or brief limited intermittent psychotic symptom$ or ((1ttenuate$ or early or premonitory or pre monitory) adj2 (sign$ or symptom$)) or predelusion$ or prehallucin$ or prepsychos$ or prepsychotic$ or preschizo$ or (pre adj (delusion$ or hallucin$ or psychos$ or psychotic$ or schizo$)) or prodrom$ or subclinical$ or sub$ clinical$ or subthreshold$ or sub$ threshold$ or at risk$ or ((high$ or incipient or 1ttenuat$) adj3 risk$)).ti,ab.
19. or/17-18
20. (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.
21. 19 and 20
22. ultra high risk.ti,ab.
23. ((at risk or ((high or increase$) adj2 risk) or blips or brief limited intermittent psychotic symptom$ or ((1ttenuate$ 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 ((1ttenuate$ or early or premonitory) adj2 (sign$ or symptom$)) or prodrom$ or

subclinical$ or sub$ clinical$ or subthreshold or sub$ threshold) adj3 (psychos$ or psychotic$ or schiz$)).ab.

24. (9 and (or/16,21-23))

1.12 CENTRAL - Wiley

| | |
|---|---|
| #1 | mesh descriptor paranoid disorders, this term only |
| #2 | mesh descriptor psychotic disorders explode all trees |
| #3 | mesh descriptor schizophrenia, childhood, this term only |
| #4 | mesh descriptor schizophrenia explode all trees |
| #5 | ("delusional disorder*" or hebephreni* or psychosis or psychoses or psychotic* or schizo*):ti or ("delusional disorder*" or hebephreni* or psychosis or psychoses or psychotic* or schizo*):ab |
| #6 | (((chronic* or serious or persistent or severe*) near/1 (mental* or psychological*) near/1 (disorder* or ill*))):ti or (((chronic* or serious or persistent or severe*) near/1 (mental* or psychological*) near/1 (disorder* or ill*))):ab or (((chronic* or serious or persistent or severe*) near/1 (mental* or psychological*) near/1 (disorder* or ill*))):kw |
| #7 | #1 or #2 or #3 or #4 or #5 or #6 |
| #8 | mesh descriptor risk factors, this term only |
| #9 | (prodrom* or symptom* or risk*):kw |
| #10 | (blips or "brief limited intermittent psychotic symptom*" or ((attenuat* or early or premonitory or "pre monitory") near/2 (sign* or symptom*)) or predelusion* or prehallucin* or prepsychos* or prepsychotic* or preschizo* or (pre near/1 (delusion* or hallucin* or psychos* or psychotic* or schizo*)) or prodrom* or subclinical* or "sub clinical*" or subthreshold* or "sub* threshold*" or "at risk*" or ((high* or incipient or increas*) near/3 risk*)):ti or (blips or "brief limited intermittent psychotic symptom*" or ((attenuat* or early or premonitory or "pre monitory") near/2 (sign* or symptom*)) or predelusion* or prehallucin* or prepsychos* or prepsychotic* or preschizo* or (pre near/1 (delusion* or hallucin* or psychos* or psychotic* or schizo*)) or prodrom* or subclinical* or "sub clinical*" or subthreshold* or "sub* threshold*" or "at risk*" or ((high* or incipient or increas*) near/3 risk*)):ab |
| #11 | #9 or #10 |
| #12 | (conversion* or ((develop* or progress*) near/2 (psychos* or psychotic* or schiz*)) or "first episode*" or fullthreshold* or "full threshold*" or onset* or progression or transition* or transitory):ti or (conversion* or ((develop* or progress*) near/2 (psychos* or psychotic* or schiz*)) or "first episode*" or fullthreshold* or "full threshold*" or onset* or progression or transition* or transitory):ab |
| #13 | #11 and #12 |
| #14 | "ultra high risk":ti or "ultra high risk":ab |
| #15 | (("at risk" or ((high or increase*) near/2 risk) or blips or "brief limited intermittent psychotic symptom*" or ((attenuat* or early or premonitory) near/2 (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*) near/2 risk) or blips or "brief limited intermittent psychotic symptom*" or ((attenuat* or early or premonitory) near/2 (sign* or symptom*)) or prodrom* or subclinical* or "sub clinical*" or subthreshold or "sub* threshold") near/3 (psychos* or psychotic* or schiz*)):ab. |
| #16 | #7 and (#8 or #13 or #14 or #15) |

## 1.2 Randomised controlled trial study design filter

Embase, Medline, PreMEDLINE, PsycINFO – OVID SP

| | |
|---|---|
| 1 | exp "clinical trial (topic)"/ or exp clinical trial/ or crossover procedure/ or double blind procedure/ or placebo/ or randomization/ or random sample/ or "randomized controlled trial (topic)"/ or single |

| | |
|---|---|
| | blind procedure/ |
| 2 | 1 use emez |
| 3 | exp clinical trial/ or exp “clinical trials as topic”/ or cross-over studies/ or double-blind method/ or placebos/ or random allocation/ or single-blind method/ |
| 4 | 3 use mesz, prem |
| 5 | (clinical trials or placebo or random sampling).sh,id. |
| 6 | 5 use psyh |
| 7 | (clinical adj2 trial$).ti,ab. |
| 8 | (crossover or cross over).ti,ab. |
| 9 | (((single$ or doubl$ or trebl$ or tripl$) adj2 blind$) or mask$ or dummy or doubleblind$ or singleblind$ or trebleblind$ or tripleblind$).ti,ab. |
| 10 | (placebo$ or random$).ti,ab. |
| 11 | treatment outcome$.md. use psyh |
| 12 | animals/ not human$.mp. use emez |
| 13 | animal$/ not human$/ use mesz, prem |
| 14 | (animal not human).po. use psyh |
| 15 | (or/2,4,6-11) not (or/12-14) |

*Appendix 2: Excluded studies*

| | Study | Reason for exclusion |
|---|---|---|
| 1 | Aminger GP, Henry LP, Harrigan SM, Harris MG, Alvarez-Jimenez M, Herrman H, et al. Outcome in early-onset schizophrenia revisited: Findings from the Early Psychosis Prevention and Intervention Centre long-term follow-up study. Schizophrenia Research 2011;131:112-119 | Design (not RCT) |
| 2 | Beaton EA., Simon TJ. How might stress contribute to increased risk for schizophrenia in children with Chromosome 22q11.2 deletion syndrome? Journal of Neurodevelopmental Disorders 2011;3(1):68-75 | No outcomes of interest |
| 3 | Cornblatt B, Lencz T, Smith CW, Olsen R, Auther AM, Nakayama E, et al. Can antidepressants be used to treat the schizophrenia prodrome? Results of prospective, naturalistic treatment study of adolescents. Journal of Clinical Psychiatry 2007;68:546-557 | Design (not RCT) |
| 4 | Correll CU. Individualizing antipsychotic treatment selection in schizophrenia: characteristics of empirically derived patient subgroups. European Psychiatry 2011;.26(Suppl. 1):3-16 | Design (not RCT) |
| 5 | Dominguez MDG, Wichers M, Lieb R, Wittchen H-U, van Os J. Evidence that onset of clinical psychosis is an outcome of progressively more persistent subclinical psychotic experiences: an 8-Year cohort study. Schizophrenia Bulletin 2011;37(1):84–93 | Design (not RCT) |
| 6 | Findling RL, McCue Horwitz S, Birmaher B, Kowatch RA, Fristad MA, Youngstrom EA et al. Clinical Characteristics of Children Receiving Antipsychotic Medication. Journal of Child and Adolescent Psychopharmacology 2011;21(4):311-319 | No outcomes of interest |
| 7 | Hulbert CA. Relationship between personality and course and outcome in early psychosis: A review of the literature. Clinical Psychology Review 1996;16(8): 707–727 | Design (not RCT) |
| 8 | Larsen TK, Melle I, Auestad B, Haahr U, Joa I, Johannessen JO, et al. Early detection of psychosis: positive effects on 5 year outcome. Psychological Medicine 2011;41:1461-1469 | Population |
| 9 | Marois MJ, Gingras N, Provencher MD, Mérette C, Emond C, Bourbeau J, et al. Cognitive-behavioural therapy in early psychosis: an open study in a clinical setting. Canadian Journal of Psychiatry 2011;56(1):51-61. | Non-English language |
| 10 | Mees,L.Z. 2011. Adolescents and young adults at ultra high risk of psychosis: detection, prediction and treatment. A review of current knowledge. Psychiatria Danubina 2011;23(Suppl. 1):S118-S122. | No outcomes of interest |
| 11 | Mittal VAT. Movement abnormalities and the progression of prodromal symptomatology in adolescents at risk for psychotic disorders. Journal of Abnormal Psychology 2007;116(2):260-267. | No outcomes of interest |
| 12 | Mortan O, Tekinsav SS, German KG. A pilot study on the effectiveness of a group-based cognitive-behavioural therapy program for coping with auditory hallucinations. Turkish Journal of Psychiatry 2011;22:26-34. | Non-English Language |
| 13 | Parellada M, Boada L, Fraguas D, Reig S, Castro-Fornieles J, Moreno D et al. Trait and state attributes of insight in first episodes of early-onset schizophrenia and other psychoses: a 2-year longitudinal study. Schizophrenia 2011;31(1):38-51 | No outcomes of interest |
| 14 | Quijada Y, Tizon JL. Early intervention in the real world: At-risk mental state (ARMS) detection in a community service center for | Design (not RCT) |

| | | |
|---|---|---|
| | early attention to psychosis in Barcelona. Early Intervention in Psychiatry 2010;4(3):257-262 | |
| 15 | Rabinowitz J, Napryeyenko O, Burba B, Martinez G; Neznanov NG, Fischel T, et al. Premorbid functioning and treatment response in recent-onset schizophrenia: prospective study with risperidone long-acting injectable. Journal of Clinical Psychopharmacology 2011;31(1):75-81. | Population |
| 16 | Ruhrmann S, Schultze-Lutter F, Salokangas RKR, Heinimaa M, Linszen D, Dingemans P et al. Prediction of psychosis in adolescents and young adults at high risk. Results from the prospective European prediction of psychosis study. Archives of General Psychiatry 2010;67(3):241-251 | Design (not RCT) |
| 17 | Schimmelmann BG, Michel C, Schaffner N, Schultze-Lutter F. What percentage of people in the general population satisfies the current clinical at-risk criteria of psychosis? Schizophrenia 2011;125(1):99-100 | Design (not RCT) |
| 18 | Wood SJY. Neuroimaging and treatment evidence for clinical staging in psychotic disorders: from the at-risk mental state to chronic schizophrenia. Biological Psychiatry 2011;70(7):619-625. | No outcomes of interest |
| *Note.*<br>*RCT=randomized controlled trial* | | |

*Appendix 3: Description of Included Psychological and Psychosocial Interventions*

| STUDY ID | INTERVENTION | DESCRIPTION |
|---|---|---|
| ADDINGTON2011 (25) | CBT | "A manualized problem-focused time limited treatment of up to 20 sessions to be completed within 6 months. This intervention was based on the experiences of the Manchester EDIE Trial in using CBT with a CHR population and specifically examined strategies for change.(63) These included normalization, generating and evaluating alternative beliefs, safety behaviours, metacognitive beliefs, core beliefs, social isolation and relapse prevention. The CBT is a formulation based approach. Treatment strategies are selected within the context of a collaboratively derived formulation and related to the problems that are agreed upon and prioritized by the client." |
| MCGORRY2002 (30, 57) | CBT | "Cognitive behaviour therapy was conducted according to a manual developed by [the authors]. The overall aims were to develop an understanding of the symptoms experienced, to learn strategies to enhance control of these symptoms, and to reduce associated distress. These strategies were drawn from mainstream CBT for nonpsychotic disorders and, where appropriate, by adapting psychological techniques that are useful in more established psychotic disorders. The following modules were offered flexibly: Stress Management, Depression/Negative Symptoms, Positive Symptoms, and Other Comorbidity (including substance abuse, obsessive-compulsive features, and social anxiety)."<br>CBT was offered for 6 months. "Varying the frequency and duration of sessions accommodated the differing needs and tolerance of the individual patients."<br>This intervention also included 1-2mg/day risperidone daily for 6 months. |
| MORRISON2004 (23, 58, 59) | CBT | "The cognitive therapy intervention was limited to a maximum of 26 sessions over 6 months and followed the principles developed by Beck.(64) It was problem oriented, time-limited and educational; it encouraged collaborative empiricism, used guided discovery and homework tasks, and was based on a written manual. It was based on the cognitive model most appropriate to the disorder that was prioritised on a problem list agreed between the therapist and the patient."<br>"The central feature of [the] approach to the prevention of psychosis involved normalising the interpretations that people make, helping them to generate and evaluate alternative explanations, decatastrophising their fears of impending madness and helping them test out such appraisals using behavioural experiments. However, if the problem prioritised was an anxiety disorder (such as panic, social phobia, obsessive–compulsive disorder or generalised anxiety) or depression, then the appropriate models were employed and a general model of emotional dysfunction was also used."<br>"Both monitoring and therapy conditions incorporated elements of case management in order to resolve crises regarding social issues and mental health risks". |
| MORRISON2011 (28, 52) | CBT | "In addition to [a] monitoring component participants allocated to [CBT] received [CBT] that is based on the specific cognitive model.(65) [CBT was] offered on a weekly basis for up to 25 weeks plus up to four booster sessions in the subsequent 6 months. [CBT] allow[ed] an individualized, problem-orientated approach within clear boundaries, and it incorporate[d] a process of assessment and formulation, which [was] manualized. The specific interventions depend[ed] on individual goals and formulations, but the range of permissible interventions is described in [a] published manual.(63) Key ingredients of the approach are the development of a problem and goal list, early formulation (both longitudinal and maintenance), a focus upon normalizing psychotic-like experiences and an active therapy stance utilizing behavioural experiments and generating evidence to test |

| | | |
|---|---|---|
| | | appraisals."<br>Participants receiving this intervention also received all the components of the monitoring control group. |
| PHILLIPS2009 (24, 60) | CBT | "This treatment draws strongly from the stress vulnerability model of psychosis(66) and emphasizes the development of strategies to cope with pre-psychotic symptomatology and life stressors. This treatment targets the unique concerns, experiences and skills of each individual and relates to a case formulation that is developed collaboratively at the start of treatment by the psychologist and patient. The treatment incorporates specific cognitive behavioural strategies that have been developed to target positive psychotic symptoms."(67-70)<br>"Psychological treatment was provided on a weekly to monthly basis depending on level of symptoms, functioning and risk. All psychology treatment sessions were 50-60 min in duration. The number of psychology sessions was not predetermined but psychologists aimed to schedule sessions weekly for the first 6 months of treatment, then fortnightly and finally monthly for the final 3 months. Therefore approximately 35 sessions was aimed at. It was recognized, however, that this schedule could not always be adhered to if the patient had high case-management needs, if symptoms resolved or if patients were unmotivated or noncompliant. Patients could not be compelled to attend sessions unless there was concern about a high risk of harm to self or someone else."<br>"In addition to providing either the cognitive therapy or [the control], psychologists also provided case management where necessary (assisting patients to address practical issues such as finding housing, arranging social security payments, enrolling in school, applying for employment and so forth) and also monitored level of risk and assisted in providing risk management and crisis intervention as needed. Family education and support was offered to all participants if deemed necessary, regardless of treatment group." |
| VANDERGAAG2012 (29, 61) | CBT | " The intervention [was] based on the protocol by French and Morrison(63) enriched with psychoeducation on dopamine and cognitive biases. Both the experimental and control groups were treated with evidence-based active treatment for the axis 1 or 2 disorder from which they were suffering. The [CBT] group was given an add-on treatment that focussed on subclinical psychosis."<br>"Education on dopamine supersensitivity [explained] how this affects perception and thinking. Furthermore, exercises were added to experience cognitive biases; becoming aware of cognitive biases may lead to corrected secondary appraisals."<br>"Behavioural goals are to consolidate school and work attendance, foster interaction with friends and relatives, and if applicable, to reduce cannabis use."<br>"[CBT] had a maximum provision of 26 weekly sessions." |
| BECHDOLF2012 (37, 39) | Integrated Therapies | *Individual CBT + skills training + cognitive remediation + psychoeducational multifamily groups:*<br>*Individual CBT* : "Based on [the authors] cognitive model(71) the individual CBT followed the basic principles of cognitive therapy described by Beck(64) as being formulation driven, structured, based on shared problems and goals, educational, utilizing guided discovery as the engine for change, involving homework and being time limited. Depending on the problems presented and the case formulation, therapists adapted the modules described in a manual"<br>*Skills training*: "Scheduling and monitoring of mastery and pleasure activities, 'keeping well' strategies, social perception and social skills training and training of problem-solving were offered in a group format. Each therapy session followed a detailed protocol which outlined the aims of the session, example interventions and model responses for the therapist" (the protocol is not cited or described further by the authors).<br>*Cognitive Remediation*: "Cognitive remediation was offered to address thought and perception deficits (basic symptoms) directly. |

| | | |
|---|---|---|
| | | It was computerized and based on cognitive exercises from the COGPACK software (Marker Software, Mannheim, Germany). In each session, three to six tasks were performed, involving repeated practice of exercises for attention, memory and executive functioning."<br>*Psychoeducational multifamily groups*: " "These groups provided information on symptoms, course and treatment of at-risk mental states, as detailed in a manual. These sessions aimed to increase the family's understanding of the EPIS and to reduce stress and interpersonal conflicts." |
| NORDENTOFT2006(35) | Integrated Therapies | " The intervention period was two years. Elements in integrated treatment were: (a) a modified Assertive Community Treatment model,(72) (b) social skills training either in groups or individually, (c) psychoeducation in multiple-family groups. Treatment elements were applied according to the individual needs of the patients." |
| RUHRMANN2007(38) | NBI | "Both conditions featured a needs-focused intervention, which, in the experimental condition, was combined with the second generation antipsychotic amisulpride. The needs-focused intervention went beyond usual clinical management because it could include psychoeducation, crisis intervention, family counselling and assistance with education or work-related difficulties, according to need. Regular psychotherapy was not provided." |
| *Note.*<br>*CBT=cognitive behavioural therapy, CHR=clinical high risk, EPIS=early initial prodromal state, NBI=Needs based intervention* | | |

*Appendix 4: Summary of Effects*

***Psychological Interventions***

***CBT Versus Supportive Counselling***

| ***Time point (months)*** | **Outcome** | **Trials in analysis** | **Participants in analysis** | **Effect Estimate (95% CI), Random-effects** | **Heterogeneity: $I^2$; $Chi^2$ (p value)** | **Quality** |
|---|---|---|---|---|---|---|
| 0-6 | Transition to psychosis (completers) (24, 25, 28, 29) | 4 (80%) | 591 (88%) | RR=0.62 (0.29 to 1.31) | 17%; 3.60 (p=0.31) | Low [1,3] |
| | Transition to psychosis (sensitivity analysis*) (24, 25, 28, 29) | 4 (80%) | 612 (91%) | RR=0.66 (0.40 to 1.08) | 0%; 2.35, (p = 0.50) | - |
| | Total symptoms (24, 25) | 2 (40%) | 123 (18%) | SMD=0.04 (-0.32 to 0.40) | 0%; 0.53(p=0.77) | Low[1,3] |

| | | | | | | |
|---|---|---|---|---|---|---|
| | Positive symptoms (24, 25, 28, 29) | 4 (80%) | 489 (73%) | SMD=-0.12 (-0.30 to 0.06) | 0%; 0.60 (p=0.90) | Moderate[3] |
| | Positive symptoms (sensitivity analysis**) (24, 25, 28) | 3 (60%) | 319 (47%) | SMD=-0.11 (-0.33 to 0.11) | 0%, 0.57 (p=0.75) | - |
| | Negative symptoms (24, 25) | 2 (40%) | 123 (18%) | SMD=0.17 (-0.19 to 0.53) | 0%; 0.38, (p= 0.54) | Low[1,3] |
| | Depression (24, 25, 28, 29) | 4 (80%) | 478 (71%) | SMD=0.13 (-0.20 to 0.47) | 67%; 9.01, (p = 0.03) | Low[2,3] |
| | Depression (sensitivity analysis**) (24, 25, 28) | 3 (60%) | 308 (46%) | SMD=0.27 (0.15 to 0.69) | 64%; 5.62 (p=0.06) | |
| | Quality of life (24, 28, 29) | 3 (60%) | 383 (57%) | SMD=0.01 (-0.19 to 0.21) | 0%; 0.8 (p=0.78) | Low[1,3] |
| | Quality of life (sensitivity analysis**) (24, 28) | 2 (40%) | 213 (32%) | SMD=0.01 (-0.26 to 0.28) | 0%; 0.08 (p=0.78) | |
| | Dropout, any reason (24, 25, 28) | 3 (60%) | 411 (61%) | RR=-1.01 (0.75 to 1.36) | 0%; 0.15 (p=0.93) | Low[1,3] |
| 6-12 | Transition to psychosis (completers) (23 -25, 28, 29) | 5 (100%) | 645 (96%) | RR=0.54 (0.34 to 0.86) | 0%; 2.51 (p=0.64) | Moderate[1] |
| | Transition to psychosis (sensitivity analysis*) (23-25, 28, 29) | 5 (100%) | 672 (100%) | RR=0.64 (0.44 to 0.93) | 0%; 2.80 (p = 0.59) | - |
| | Total symptoms(23- 25) | 3 (60%) | 154 (23%) | SMD=0.05 (-0.27 to 0.37) | 0%; 0.45 (p=0.08) | Low[1,3] |
| | Positive symptoms (23-25, 28, 29) | 5 (100%) | 493 (73%) | SMD=-0.17 (-0.35 to 0.01) | 0%; 3.53 (p = 0.47) | Moderate[3] |
| | Positive symptoms (sensitivity analysis**) (23- | 4 (80%) | 342 (51%) | SMD=-0.27 (-0.49 to -0.06) | 0%, 0.94 (p=0.82) | - |

| | | | | | | |
|---|---|---|---|---|---|---|
| | 25, 28) | | | | | |
| | Negative symptoms (23-25) | 3 (60%) | 154 (23%) | SMD=0.11 (-0.21 to 0.43) | 0%; 0.11 (p = 0.95) | Low[1,3] |
| | Depression (25, 28, 29) | 3 (60%) | 385 (57%) | SMD=-0.05 (-0.25, 0.15) | 0%; 0.92 (p=0.63) | Low[1,3] |
| | Depression (sensitivity analysis**) (25, 28) | 2 (40%) | 234 (35%) | SMD=-0.01 (-0.26 to 0.25) | 0%; 0.61 (p=0.43) | - |
| | Quality of life (24, 28, 29) | 3 (60%) | 329 (26%) | SMD=-0.01 (-0.23 to 0.21) | 0%; 0.56 (p=0.75) | Low[1,3] |
| | Quality of life (sensitivity analysis**) (24, 28) | 2 (40%) | 178 | SMD=-0.05 (-0.35 to 0.25) | 0%; 0.40 (p=0.53) | - |
| | Dropout, any reason (23-25, 28, 29) | 5(100%) | 665 (99%) | RR=1.03 (0.82 to 1.30) | 0%; 1.50 (p=0.83) | Low[1,3] |
| After 12 | Transition to psychosis (completers) (23, 25, 28, 29) | 4 (80%) | 570 (85%) | RR=0.63 (0.40 to 0.99) | 0%; 2.50 (p=0.48) | Low[1,3] |
| | Transition to psychosis (sensitivity analysis*) (23, 25, 28, 29) | 4 (80%) | 595 (89%) | RR=0.55 (0.25, 1.19) | 79%; 14.48 (p=0.002) | - |
| | Total symptoms (25) | 1 (20%) | 51 (8%) | SMD=-0.04 (-0.59 to 0.51) | NA | Low[1,3] |
| | Positive symptoms (25, 28, 29) | 3 (60%) | 256 (38%) | SMD=-0.17 (-0.42 to 0.07) | 0%; 0.66 (p = 0.72) | Low[1,3] |
| | Positive symptoms (sensitivity analysis **) (25, 28) | 2 (40%) | 116 (17%) | SMD=-0.14 (-0.50 to 0.23) | 0%, 0.58 (p=0.45) | - |
| | Negative symptoms (25) | 1 (20%) | 51 (8%) | SMD=-0.10 (-0.65 to 0.45) | NA | Low[1,3] |

| | | | | | | |
|---|---|---|---|---|---|---|
| | Depression (25, 28, 29) | 3 (60%) | 352 (52%) | SMD=-0.11 (-0.36 to 0.13) | 0%; 1.44 (p=0.49) | Low[1,3] |
| | Depression (sensitivity analysis**) (25, 28) | 2 (40%) | 112 (175) | SMD=-0.05 (-0.46 to 0.37) | 19%; 1.24 (p=0.27) | - |
| | Quality of life (28, 29) | 2 (40%) | 188 (28%) | SMD=0.18 (-0.10 to 0.47) | 0%, 0.73 (p=0.39) | Low[1,3] |
| | Quality of life (sensitivity analysis**) (28) | 1 (10%) | 48 (7%) | SMD=0.40 (-0.17 to 0.98) | NA | - |
| | Dropout, any reason (23, 25, 28, 29) | 4 (80%) | 593 (88%) | RR=1.09 (0.88 to 1.35) | 0%; 1.95 (p=0.58) | Low[1,3] |

***CBT Plus Risperidone Versus Supportive Counselling***

| ***Time point (months)*** | **Outcome** | **Trials in analysis** | **Participants in analysis** | **Effect Estimate (95% CI), Random-effects** | **Heterogeneity: $I^2$; $Chi^2$ (p value)** | **Quality** |
|---|---|---|---|---|---|---|
| 0-6 | Transition to psychosis (completers) (24, 30) | 2 (100%) | 130 (100%) | RR=0.35 (0.13 to 0.95) | 0%; 0.59 (p=0.44) | Very low[1,3,4] |
| | Total symptoms (24, 30) | 2 (100%) | 102 (78%) | SMD=0.15 (-0.39 to 0.70) | 59%; 2.43 (p=0.12) | Very low[1,3,4] |
| | Positive symptoms (24, 30) | 2 (100%) | 130 (100%) | SMD=0.02 (-0.33 to 0.37) | 0%; 0.72 (p = 0.39) | Very low[1,3,4] |
| | Negative symptoms (24, 30) | 2 (100%) | 130 (100%) | SMD=0.13 (-0.68 to 0.94) | 81%; 5.26 (p = 0.02) | Very low[1,2,3,4] |
| | Depression (24, 30) | 2 (100%) | 130 (100%) | SMD=0.24 (-0.12 to 0.59) | 88%; 8.36 (p=0.003) | Very low[1,3,4] |
| | Mania (30) | 1 (50%) | 59 (45%) | SMD=-0.20 (-0.71 to 0.32) | NA | Very low[1,3,4] |
| | Quality of life (24, 30) | 2 (100%) | 130 (100%) | SMD=-0.13 (-0.49 to 0.22) | 2%; 1.02 (p=0.31) | Very low[1,3,4] |
| | Dropout, any reason (24, 30) | 2 (100%) | 130 (100%) | RR=0.76 (0.28 to 2.03) | NA | Very low[1,3,4] |

| | | | | | | |
|---|---|---|---|---|---|---|
| 6-12 | Transition to psychosis (completers) (24, 30) | 2 (100%) | 130 (100%) | RR=0.63 (0.33 to 1.21) | 0%; 0.25 (p=0.61) | Very low[1,3,4] |
| | Total symptoms (24, 30) | 2 (100%) | 101 (78%) | SMD=0.07 (-0.32 to 0.46) | 0%; 0.73 (p=0.39) | Very low[1,3,4] |
| | Positive symptoms (24, 30) | 2 (100%) | 101 (78%) | SMD=0.05 (-0.35 to 0.44) | 0%; 0.90 (p = 0.34) | Very low[1,3,4] |
| | Negative symptoms (24, 30) | 2 (100%) | 101 (78%) | SMD=0.08 (-0.31 to 0.47) | 0%; 0.67 (p = 0.41) | Very low[1,3,4] |
| | Depression (24, 30) | 2 (100%) | 68 (52%) | SMD=0.15 (-0.33 to 0.62) | 0%, 0.01 (p=0.93) | Very low[1,3,4] |
| | Mania (30) | 1 (50%) | 59 (45%) | SMD=0.00 (-0.51 to 0.51) | NA | Very low[1,3,4] |
| | Quality of life (24, 30) | 2 (100%) | 102 (78%) | SMD=-0.07 (-0.46 to 0.32) | 0%; 0.04 (p=0.84) | Very low[1,3,4] |
| | Dropout, any reason (24, 30) | 2 (100%) | 130 (100%) | SMD=0.85 (0.43 to 1.67) | 43%; 1.75 (p=0.19) | Very low[1,3,4] |
| After 12 | Transition to psychosis (completers) (30) | 1 (50%) | 41 (32%) | RR=0.59 (0.34 to 1.04) | NA | Very low[1,3,4] |
| | Transition to psychosis (sensitivity analysis*) (30) | 1 (50%) | 59 (45%) | RR=0.67 (0.46 to 0.96) | NA | - |
| | Total symptoms (30) | 1 (50%) | 41 (32%) | SMD=-0.33 (-0.96 to 0.29) | NA | Very low[1,3,4] |
| | Positive symptoms (30) | 1 (50%) | 41 (32%) | SMD=-0.04 (-0.66 to 0.58) | NA | Very low[1,3,4] |
| | Negative symptoms (30) | 1 (50%) | 41 (32%) | SMD=-0.24 (-0.87 to 0.38) | NA | Very low[1,3,4] |
| | Depression (30) | 1 (50%) | 41 (32%) | SMD=0.23 (-0.39 to 0.86) | NA | Very low[1,3,4] |
| | Mania (30) | 1 (50%) | 41 (32%) | SMD=-0.36 (-0.98 to 0.27) | NA | Very low[1,3,4] |

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| | Quality of life (30) | 1 (50%) | 41 (32%) | SMD=0.08 (-0.54 to 0.71) | NA | Very low[1,3,4] |
| | Dropout, any reason (30) | 1 (50%) | 59 (45%) | RR=0.57 (0.26 to 1.28) | NA | Very low[1,3,4] |

***Integrated Psychotherapy Versus Supportive Counselling***

| ***Time point (months)*** | **Outcome** | **Trials in analysis** | **Participants in analysis** | **Effect Estimate (95% CI), Random-effects** | **Heterogeneity: $I^2$; $Chi^2$ (p value)** | **Quality** |
|---|---|---|---|---|---|---|
| 6-12 | Transition to psychosis (completers) (37) | 1 (100%) | 125 (100%) | RR=0.19 (0.04 to 0.81) | NA | Very Low[1,3,5] |
| | Dropout, any reason (37) | 1 (100%) | 128 (100%) | RR=1.55 (0.68 to 3.53) | NA | Very Low[1,3,5] |
| After 12 | Transition to psychosis (completers) (37) | 1 (100%) | 125 (100%) | RR=0.32 (0.11 to 0.92) | NA | Very Low[1,3,5] |
| | Dropout, any reason (37) | 1 (100%) | 128 (100%) | RR=0.95 (0.61 to 1.49) | NA | Very Low[1,3,5] |

***Integrated Psychotherapy Versus Standard care***

| ***Time point (months)*** | **Outcome** | **Trials in analysis** | **Participants in analysis** | **Effect Estimate (95% CI), Random-effects** | **Heterogeneity: $I^2$; $Chi^2$ (p value)** | **Quality** |
|---|---|---|---|---|---|---|
| 6-12 | Transition to psychosis (completers) (35) | 1 (100%) | 67 (85%) | RR=0.24 (0.07 to 0.81) | NA | Low[1,3] |
| | Transition to psychosis (sensitivity analysis*) (35) | 1 (100%) | 79 (100%) | RR=0.41 (0.20 to 0.85) | NA | - |
| | Positive symptoms (35) | 1 (100%) | 62 (78%) | SMD=-0.30 (-0.76 to 0.16) | NA | Low[1,3] |
| | Dropout, any reason (35) | 1 (100%) | 79 (100%) | RR=0.63 (0.22 to 1.81) | NA | Low[1,3] |
| After 12 | Transition to psychosis (completers) (35) | 1 (100%) | 65 (82%) | RR=0.52 (0.26 to 1.02) | NA | Low[1,3] |

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|---|---|---|---|---|---|---|
| | Transition to psychosis (sensitivity analysis*) (35) | 1 (100%) | 79 (100%) | RR=0.60 (0.37 to 0.98) | NA | - |
| | Positive symptoms (35) | 1 (100%) | 57 (72%) | SMD=-0.36 (-0.89 to 0.16) | NA | Low[1,3] |
| | Negative symptoms (35) | 1 (100%) | 57 (72%) | SMD=-0.42 (-1.09 to 0.25) | NA | Low[1,3] |
| | Dropout, any reason (35) | 1 (100%) | 79 (100%) | RR=0.66 (0.25 to 1.73) | NA | Low[1,3] |

***Pharmacological Interventions***

***CBT Plus Risperidone Versus CBT Plus Placebo***

| ***Time point (months)*** | **Outcome** | **Trials in analysis** | **Participants in analysis** | **Effect Estimate (95% CI), Random-effects** | **Heterogeneity: $I^2$; $Chi^2$ (p value)** | **Quality** |
|---|---|---|---|---|---|---|
| 0-6 | Transition to psychosis (completers) (24) | 1 (100%) | 87 (100%) | RR=1.02 (0.15 to 6.94) | NA | Very low[1,3,4] |
| | Total symptoms (24) | 1 (100%) | 87 (100%) | SMD=0.32 (-0.11 to 0.74) | NA | Very low[1,3,4] |
| | Positive symptoms (24) | 1 (100%) | 87 (100%) | SMD=0.37 (-0.05 to 0.80) | NA | Very low[1,3,4] |
| | Negative symptoms (24) | 1 (100%) | 87 (100%) | SMD=0.29 (-0.13 to 0.72) | NA | Very low[1,3,4] |
| | Depression (24) | 1 (100%) | 87 (100%) | SMD=0.16 (-0.26 to 0.58) | NA | Very low[1,3,4] |
| | Quality of life (24) | 1 (100%) | 87 (100%) | SMD=-0.25 (-0.67 to 0.18) | NA | Very low[1,3,4] |
| | Dropout, any reason (24) | 1 (100%) | 87 (100%) | RR=0.80 (0.33 to 1.95) | NA | Very low[1,3,4] |
| 6-12 | Transition to psychosis (completers) (24) | 1 (100%) | 56 (64%) | RR=1.02 (0.39 to 2.67) | NA | Very low[1,3,4] |

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|---|---|---|---|---|---|---|
| | Total symptoms (24) | 1 (100%) | 51 (59%) | SMD=-0.24 (-0.79 to 0.31) | NA | Very low[1,3,4] |
| | Positive symptoms (24) | 1 (100%) | 51 (59%) | SMD=-0.07 (-0.62 to 0.48) | NA | Very low[1,3,4] |
| | Negative symptoms (24) | 1 (100%) | 51 (59%) | SMD=0.12 (-0.43 to 0.67) | NA | Very low[1,3,4] |
| | Depression (24) | 1 (100%) | 9 (10%) | SMD=-0.29 (-1.61 to 1.04) | NA | Very low[1,3,4] |
| | Quality of life (24) | 1 (100%) | 51 (59%) | SMD=-0.23 (-0.78 to 0.33) | NA | Very low[1,3,4] |
| | Dropout, any reason (24) | 1 (100%) | 87 (100%) | RR=1.09 (0.62 to 1.92) | NA | Very low[1,3,4] |

***Olanzapine Versus Placebo***

| ***Time point (months)*** | **Outcome** | **Trials in analysis** | **Participants in analysis** | **Effect Estimate (95% CI), Random-effects** | **Heterogeneity: $I^2$; $Chi^2$ (p value)** | **Quality** |
|---|---|---|---|---|---|---|
| 0-6 | Total symptoms (54) | 1 (100%) | 59 (99%) | SMD=-0.29 (-0.80 to 0.22) | NA | Very Low[1,3,4] |
| | Positive symptoms (54) | 1 (100%) | 59 (99%) | SMD=-0.47 (-0.99 to 0.05) | NA | Very Low[1,3,4] |
| | Negative symptoms (54) | 1 (100%) | 59 (99%) | SMD=-0.07 (-0.58 to 0.44) | NA | Very Low[1,3,4] |
| | Depression (54) | 1 (100%) | 59 (99%) | SMD=0.08 (-0.43 to 0.60) | NA | Very Low[1,3,4] |
| | Mania (54) | 1 (100%) | 59 (99%) | SMD=-0.40 (-0.92 to 0.11) | NA | Very Low[1,3,4] |
| | Dropout, any reason (54) | 1 (100%) | 60 (100%) | RR=1.29 (0.60 to 2.74) | NA | Very Low[1,3,4] |
| | Weight gain (54) | 1 (100%) | 59 (99%) | SMD=0.81 (0.28 to 1.34) | NA | Very Low[1,3,4] |

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| 6-12 | Transition to psychosis (54) | 1 (100%) | 60 (100%) | RR=0.43 (0.17 to 1.08) | NA | Very Low[1,3,4] |
| | Total symptoms (54) | 1 (100%) | 59 (99%) | SMD=-0.12 (-0.63 to 0.39) | NA | Very Low[1,3,4] |
| | Positive symptoms (54) | 1 (100%) | 59 (99%) | SMD=-0.40 (-0.91 to 0.12) | NA | Very Low[1,3,4] |
| | Negative symptoms (54) | 1 (100%) | 59 (99%) | SMD=0.05 (-0.46 to 0.56) | NA | Very Low[1,3,4] |
| | Depression (54) | 1 (100%) | 59 (99%) | SMD=0.32 (-0.19 to 0.83) | NA | Very Low[1,3,4] |
| | Mania (54) | 1 (100%) | 59 (99%) | SMD=-0.15 (-0.66 to 0.36) | NA | Very Low[1,3,4] |
| | Dropout, any reason (54) | 1 (100%) | 60 (100%) | RR=1.59 (0.88 to 2.88) | NA | Very Low[1,3,4] |
| | Dropout, side effect (54) | 1 (100%) | 60 (100%) | RR=0.94 (0.06 to 14.27) | NA | Very Low[1,3,4] |
| | Weight gain (54) | 1 (100%) | 59 (99%) | SMD=1.18 (0.62 to 1.73) | NA | Very Low[1,3,4] |

***Amisulpride + "Needs Base Intervention" versus "Needs Base Intervention"***

| ***Time point (months)*** | **Outcome** | **Trials in analysis** | **Participants in analysis** | **Effect Estimate (95% CI), Random-effects** | **Heterogeneity: $I^2$; $Chi^2$ (p value)** | **Quality** |
|---|---|---|---|---|---|---|
| 0-6 | Total symptoms (38) | 1 (100%) | 102 (82%) | SMD=-0.36 (-0.75 to 0.04) | NA | Very Low[1,3,4] |
| | Positive symptoms (38) | 1 (100%) | 102 (82%) | SMD=-0.53 (-0.93 to -0.13) | NA | Very Low[1,3,4] |
| | Negative symptoms (38) | 1 (100%) | 102 (82%) | SMD=-0.26 (-0.65 to 0.14) | NA | Very Low[1,3,4] |
| | Depression (38) | 1 (100%) | 102 (82%) | SMD=-0.51 (-0.91 to -0.11) | NA | Very Low[1,3,4] |

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|---|---|---|---|---|---|---|
| | Dropout, any reason (38) | 1 (100%) | 124 (100%) | RR=0.59 (0.38 to 0.94) | NA | Very Low[1,3,4] |
| | Dropout, side effect (38) | 1 (100%) | 124 (100%) | RR=6.36 (0.34 to 120.67) | NA | Very Low[1,3,4] |

***Nutritional Supplements***

***Omega-3 Fatty Acids Versus Placebo***

| ***Time point (months)*** | **Outcome** | **Trials in analysis** | **Participants in analysis** | **Effect Estimate (95% CI), Random-effects** | **Heterogeneity: $I^2$; $Chi^2$ (p value)** | **Quality** |
|---|---|---|---|---|---|---|
| 0-6 | Transition to psychosis (completers) (26) | 1 (100%) | 76 (94%) | RR=0.13 (0.02 to 0.95) | NA | Low[1,4] |
| | Transition to psychosis (sensitivity analysis*) (26) | 1 (100%) | 81 (100%) | RR=0.39 (0.13 to 1.14) | NA | - |
| 6-12 | Transition to psychosis (26) | 1 (100%) | 81 (100%) | RR=0.18 (0.04 to 0.75) | NA | Low[1,4] |
| | Total symptoms (26) | 1 (100%) | 81 (100%) | SMD=-1.26 (-1.74 to -0.78) | NA | Low[1,4] |
| | Positive symptoms (26) | 1 (100%) | 81 (100%) | SMD=-2.08 (-2.63 to -1.54) | NA | Low[1,4] |
| | Negative symptoms (26) | 1 (100%) | 81 (100%) | SMD=-2.22 (-2.77 to -1.66) | NA | Low[1,4] |
| | Depression (26) | 1 (100%) | 81 (100%) | SMD=-0.56 (-1.01 to -0.12) | NA | Low[1,4] |
| | Dropout, any reason (26) | 1 (100%) | 81 (100%) | RR=1.46 (0.26 to 8.30) | NA | Low[1,4] |

*Note.*
*For each intervention the following outcomes were extracted if reported in the study: transition to psychosis, total symptoms, positive symptoms, negative symptoms, depression, mania, quality of life, drop out for any reason, drop out due to side effects and weight gain.*
** The sensitivity analysis assumed dropouts transitioned to psychosis*
*** The sensitivity analysis excluded VANDERGAAG2012*

*Reasons for downgrading: [1]imprecision, [2]inconsistency, [3]risk of bias, [4]risk of publication bias, [5]indirectness*