TECHNICAL COMMENTARY

Outcomes of first-episode psychosis and high-risk mental states

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Introduction

After being identified as having high-risk (prodromal) mental states, or after an initial diagnosis of first-episode psychosis or schizophrenia, outcomes over the years following include symptom severity, recovery and remission, relapse, employment, functioning, relationships, and quality of life. Investigating these outcomes and the factors influencing them provides an insight into early treatment strategies.

Method

We have included only systematic reviews (systematic literature search, detailed methodology with inclusion/exclusion criteria) published in full text, in English, from the year 2000 that report results separately for people with a diagnosis of schizophrenia, schizoaffective disorder, schizophreniform disorder or first episode schizophrenia. Reviews were identified by searching the databases MEDLINE, EMBASE, CINAHL, Current Contents, PsycINFO and the Cochrane library. Hand searching reference lists of identified reviews was also conducted. When multiple copies of reviews were found, only the most recent version was included. Reviews with pooled data are prioritised for inclusion.

Review reporting assessment was guided by the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) checklist that describes a preferred way to present a meta-analysis[1]. Reviews with less than 50% of items checked have been excluded from the library. The PRISMA flow diagram is a suggested way of providing information about studies included and excluded with reasons for exclusion. Where no flow diagram has been presented by individual reviews, but identified studies have been described in the text, reviews have been checked for this item. Note that early reviews may have been guided by less stringent reporting checklists than the PRISMA, and that some reviews may have been limited by journal guidelines.

Evidence was graded using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) Working Group approach where high quality evidence such as that gained from randomised controlled trials (RCTs) may be downgraded to moderate or low if review and study quality is limited, if there is inconsistency in results, indirect comparisons, imprecise or sparse data and high probability of reporting bias. It may also be downgraded if risks associated with the intervention or other matter under review are high. Conversely, low quality evidence such as that gained from observational studies may be upgraded if effect sizes are large, there is a dose dependent response or if results are reasonably consistent, precise and direct with low associated risks (see end of table for an explanation of these terms)[2]. The resulting table represents an objective summary of the available evidence, although the conclusions are solely the opinion of staff of NeuRA (Neuroscience Research Australia).

Results

We found 12 reviews that met our inclusion criteria[3-14].

- Moderate quality evidence suggests that following a first episode of psychosis, up to 80% of people have good or intermediate outcomes for up to 3 years. Positive outcomes include lack of relapse or rehospitalisation, more employment, more insight and clarity, and improved relationships with family and friends. Predictors of good outcome include being treated with a combination of pharmacotherapy and psychosocial therapy and being from a developing rather than a developed country. Predictors of poor outcome include being treatment naive at

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study entry, being medicated with first, rather than second generation antipsychotics, and having depressive symptoms.

- Moderate to high quality evidence suggests a significant, small effect of worse positive and depressive symptoms, and worse global functioning in people with first-episode schizophrenia who have a current substance use disorder (SUD) compared to people with first-episode schizophrenia who have a former SUD. Moderate quality evidence also finds an increased risk of treatment non-adherence, relapse and re-hospitalisation, particularly if abusing cocaine, opiates, or ecstasy.
- Moderate quality evidence indicates the average risk of transition to full psychotic episode in people at high clinical risk of psychosis is 24-29%. An older mean age at baseline was associated with lower transition rates in studies with longer follow-up (>1 year), although studies with older samples in general reported higher transition rates than studies with younger samples. More recent publications reported lower transition rates than older publications. Studies offering psychosocial treatments or antipsychotics reported lower transition rates than studies offering standard care or no antipsychotics.
- Moderate quality evidence suggests people with brief limited intermittent psychotic symptoms had higher transition to psychosis rates by the 1-4 year follow-up than people with attenuated psychotic symptoms. People with attenuated psychotic symptoms had higher transition to psychosis rates than people with genetic risk and deterioration syndrome, who had similar transition rates to people with no clinical risk.
- Moderate quality evidence suggests greater risk of psychotic recurrence by 2-3 year follow-up in people with first-episode psychosis than in people with acute and transient psychotic disorder, brief psychotic disorder, brief intermittent psychotic symptoms, or brief limited intermittent psychotic symptoms.
- Moderate quality evidence suggests neurocognitive deficits, negative, and disorganisation symptoms are associated with poor functioning in people with high-risk mental states.
- Moderate to high quality evidence suggests people at high-risk of psychosis have a large impairment in functioning and a small impairment in quality of life compared to healthy controls. Conversely, people at high-risk of psychosis have a small to medium-sized effect of better functioning than people with psychosis. People at high-risk who go on to develop psychosis show a medium-sized effect of poorer functioning than people at high-risk who do not develop psychosis.

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Allott K, Liu P, Proffitt T, Killackey E

Cognition at illness onset as a predictor of later functional outcome in early psychosis: Systematic review and methodological critique

Schizophrenia Research 2011; 125: 221-235

View review abstract online

Comparison	**Cognitive predictors of functional outcome.**
Summary of evidence	**Moderate quality evidence (large sample, unable to assess consistency or precision, direct) suggests reasoning and problem solving ability were most frequently predictive of good functional outcome. General cognition, verbal/language skills, verbal learning and memory were less frequently predictive, and motor skills, working memory, verbal fluency, visual learning, memory, construction and visuospatial skills were not predictive of functional outcome.**
Functional outcome **Measured by a self-report or interviewer-rated scale of community functioning or a measure of 'real world' community functioning (e.g., job tenure)**	
22 studies, N = 1,817 Taking the following methodological factors into consideration (potential confounding factors, study follow-up periods, study power and attrition rates), it was found that reasoning and problem-solving ability were most frequently predictive of functional outcome. Three other cognitive domains that were consistently associated with functional outcome were global/general cognition, verbal/language skills and verbal learning and memory. Other cognitive domains were found to have comparatively poor predictive value with functional outcome, including motor skills, working memory, verbal fluency, visual learning and memory, and construction and visuospatial skills.	
Consistency in results‡	Unable to assess; no measure of consistency is reported.
Precision in results§	Unable to assess; no measure of precision is reported.
Directness of results‖	Direct

Archie S, Gyomorey K

First episode psychosis, substance abuse and prognosis: A systematic review

Current Psychiatry Reviews 2009; 5: 153-163

View review abstract online

Comparison	**People with first-episode psychosis (FEP) and a substance use disorder (SUD) vs. people with FEP and no SUD.**
Summary of evidence	**Moderate quality evidence (medium to large samples, appears inconsistent, unable to assess precision, direct) suggests an increased risk of relapse and re-hospitalisation in people with FEP and a SUD, particularly if abusing cocaine, opiates, or ecstasy, as well as increased treatment non-compliance. There may also increased severity of positive symptoms and decreased severity of negative symptoms.**

Risk of relapse

Measured by chart records, BPRS, clinical judgement

2 prospective cohort studies (N = 223; 12 to 15 month follow up), showed significantly increased rate of relapse in people with FEP and a SUD, with the rate increasing with increasing substance abuse.

Risk of re-hospitalisation

Measured by chart records, BPSR, SAPS, SANS, GAF, PSE-9, CATEGO-DHA, # of hospital days, days with insufficient compliance, DAS-M (employment/rehab/school), life cart admissions, occupational and residential status

2 out of 4 studies (N = 451) found the rate of re-hospitalisation was significantly higher in people with FEP and a SUD. The rate increased with the severity of substance abuse, particularly for abuse of cocaine, opiates and ecstasy, but not alcohol.

Positive symptoms

Measured by chart records, BPRS, SAP, SANS, GAF, working/in school, PSE-9, CATEGO-DHA, DAS-M, cognitive battery, PANSS, QLS, MADRS, CGI

5 studies (N = 915) found a significant increase in positive symptom severity in people with FEP and a SUD. 2 studies found this effect was specific to cannabis and absent for alcohol.

2 studies (N = 302) found no differences in positive symptoms.

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Negative symptoms **Measured by chart records, BPRS, SANS, QLS, SOFAS, LCS, GAF, SAP, PSE-9, CATEGO-DHA, DAS-M, PANSS, MADRS, CGI, cognitive battery**	
7 studies (N = 1,499) found a trend effect for decreased negative symptom severity in people with FEP and a SUD. 1 RCT (N = 262) found increased negative symptom severity in people with FEP and a SUD.	
Medication compliance **Measured by BPRS, clinical judgment for medication compliance, SAPS, SANS, GAF, taking medication at 6 months, dropout rate, SADS, PANSS, MADRS, CGI, days with at least one pill**	
3 studies (N = 432) found poorer treatment compliance in people with FEP and a SUD. Greater cannabis use reportedly increased non-compliance. 2 studies (N = 299) found no significant difference in compliance rates.	
Employment, social and cognitive function	
1 study (N = 126) found poorer social function and quality of life in people with FEP and a SUD. 2 studies (N = 1,607) found no significant difference in functioning.	
Consistency in results	Appears inconsistent.
Precision in results	Unable to assess; no measure of precision is reported.
Directness of results	Direct

Cotter J, Drake RJ, Bucci S, Firth J, Edge D, Yung AR

What drives poor functioning in the at-risk mental state? A systematic review

Schizophrenia Research 2014; 159: 267–277

View review abstract online

Comparison	**Factors predicting functioning in people with high-risk mental states.**
Summary of evidence	**Moderate quality evidence (large sample, appears consistent, unable to assess precision, direct) suggests negative**

	symptoms, disorganisation and neurocognitive deficits were consistently associated with poor functioning. Functional disability was unrelated to psychotic symptoms.
Functioning, defined as the frequency of, quality of, or satisfaction with social, academic or occupational activity	
72 studies, N = 6,011 Negative symptoms, disorganisation and neurocognitive deficits were consistently associated with poor functioning. Functional disability was unrelated to positive psychotic symptoms. A supportive family environment and high personal resilience may help minimise functional impairment.	
Consistency in results	Authors report the findings to be largely consistent.
Precision in results	Unable to assess; no measure of precision is reported.
Directness of results	Direct

Fusar-Poli P, Bonoldi I, Yung AR, Borgwardt S, Kempton MJ, Valmaggia L, Barale F, Caverzasi E, McGuire P

Predicting psychosis: meta-analysis of transition outcomes in individuals at high clinical risk

Archives of General Psychiatry 2012; 69(3): 220-229

View review abstract online

Comparison	**Transition to psychosis in people at high clinical risk for psychosis.**
Summary of evidence	**Moderate quality evidence (large samples, inconsistent, unable to assess precision, direct) indicates the mean risk of transition to full psychotic episode in clinical high-risk groups is 29.2%. Studies with older samples reported higher transition rates than studies with younger samples, and more recent publications reported lower transition rates than older publications. Studies offering psychosocial treatments or antipsychotics reported lower transition rates than studies offering standard care or no antipsychotics.**
Transition to psychotic episode	

27 studies, N = 2,502

Overall, the mean transition risk to a full psychotic episode from a clinical high risk state was 29.2%, with a mean follow-up of 31 months after initial presentation;

29.2%, 95%CI 27.3% to 31.1%, I^2 = 83.11%, Q_W = 204.48, $p < 0.001$

Removing studies with quality ratings in the lowest 30% decreased the overall estimate of transition risk to 22%.

6 months after initial presentation transition risk = 18%

1 year after initial presentation transition risk = 22%

2 years after initial presentation transition risk = 29%

3 years after initial presentation transition risk = 36%

Meta-regression revealed a significant, medium-sized relationship of increasing mean age with increasing mean risk of transition to psychosis;

$\beta = 0.07$, 95%CI 0.05 to 0.09, $p < 0.001$, Q = 27.94, $p < 0.001$

Meta-regression revealed a significant, medium-sized relationship with more recent publications reporting lower transition risks;

$\beta = -0.15$, 95%CI -0.17 to -0.11, $p < 0.001$

No effect of sex was found for risk of transition to psychosis;

$\beta = 0.002$, 95%CI -0.08 to 0.12, $p = 0.88$

Studies using the Basic Symptoms (BS) approach to define high-risk (subjective disturbances of cognitive processing and the perception of the self and the world) reported higher transition rates (but high variability) compared to studies using the Ultra High Risk (UHR) approach (either attenuated psychotic symptoms, full-blown psychotic symptoms that are brief and self-limiting, or a significant decrease in functioning in the context of a genetic risk for schizophrenia);

BS: 2 studies, 48.5%, 95%CI 41.9% to 55.9%, I^2 = 96.96, $p < 0.001$

UHR: 22 studies, 27.7%. 95%CI 25.6% to 29.9%

Both: 3 studies, 22.5%, 95%CI 18.4% to 27.3%

$Q_B = 46.56$, $p < 0.001$

No differences were reported between studies defining high-risk using the Structured Interview for Prodromal Syndromes (SIPS) or the Comprehensive Assessment of At-Risk Mental States (CAARMS);

SIPS: 28.1%, 95%CI 25.1% to 31.3%

CAARMS: 27.4%, 95%CI, 24.6% to 30.4%

$Q_B = 0.12$, $p = 0.73$

Studies using standard classification to define transition to psychosis (ICD-10, DSM-III, or DSM-IV) reported a large variance in the risk estimates across studies;

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Mean transition risk estimate: 51.1%, 95%CI 43.4% to 58.7%, I^2 = 97.23 *No differences were reported in studies defining "transition" using the SIPS or the CAARMS;* SIPS: 27.5%, 95% CI 24.3% to 30.9% CAARMS: 27.3%, 95% CI, 25.0% to 29.7% Q_B = 0.008, *p* = 0.93 *Studies of patients receiving psychosocial treatments (e.g. cognitive behavioral therapy; CBT) reported lower mean transition risk than studies of patients receiving standard care (e.g. case management);* CBT: 24.9%, 95%CI, 23.2% to 28.0% Standard care: 32.8%, 95% CI, 29.5% to 36.2% Q_B = 11.69, *p* < 0.001 *Studies of patients taking antipsychotics reported lower mean transition risk than studies of patients not exposed to antipsychotics;* Antipsychotics: 22.9%, 95% CI 20.5% to 25.5% No antipsychotics: 36.5%, 32.1% to 41.3% Q_B = 28.32, *p* < 0.001	
Consistency in results	Inconsistent where reported.
Precision in results	Unable to assess; no measure of precision is reported.
Directness of results	Direct

Fusar-Poli P, Rocchetti M, Sardella A, Avila A, Brandizzi M, Caverzasi E, Politi P, Ruhrmann S, McGuire P

Disorder, not just state of risk: meta-analysis of functioning and quality of life in people at high risk of psychosis

The British Journal of Psychiatry 2015; 207: 198-206

View review abstract online

Comparison 1	**Functioning and quality of life in people with high-risk mental states vs. controls and vs. people with psychosis.**
Summary of evidence	**Moderate to high quality evidence (large samples, inconsistent, precise, direct) suggests people at high-risk of psychosis have a large impairment in functioning and a small impairment in**

	quality of life compared with healthy controls. People at high-risk of psychosis have a small to medium-sized effect of better functioning than people with psychosis.
Functioning	
People at high-risk of psychosis had a large impairment in functioning compared with healthy controls; 18 studies, N = 3012, *g* = -3.01, 95%CI -3.68 to -2.34, *p* < 0.001, I^2 = 96.6%, *p* < 0.001 Meta-regression found that higher proportion of females in the healthy control group was correlated with lower magnitude of the effect size. There were no associations between level of functioning and proportion of females or males in the high-risk group, age, publication year, or study quality. *People at high-risk of psychosis had a small to medium-sized effect of better functioning than people with psychosis;* 14 studies, *g* = 0.34, 95%CI 0.07 to 0.60, *p* = 0.012, I^2 = 79.5%, *p* < 0.001 Meta-regression revealed better functioning in women in both the high-risk and psychosis groups. There were no associations with age or publication year. Authors report no publication bias.	
Quality of life	
People at high-risk had a small effect of poorer quality of life than the healthy control group; 4 studies, N = 945, *g* = -1.75, 95%CI -2.83 to -0.67, *p* = 0.001, I^2 = 96.7%, *p* < 0.001 *People at high-risk had similar quality of life as people with psychosis;* 3 studies, g = 0.02, 95%CI -0.64 to 0.67, *p* = 0.958, I^2 = 87.6%, *p* < 0.001	
Consistency in results	Inconsistent
Precision in results	Precise
Directness of results	Direct
Comparison 2	**Baseline functioning in people with high-risk mental states who later transition to psychosis vs. people with high-risk mental states who do not transition to psychosis.**
Summary of evidence	**Moderate to high quality evidence suggests (large samples, inconsistent, precise, direct) that among the high-risk group, those who did not develop psychosis reported a medium-sized effect of better functioning than those who did develop psychosis.**

Baseline functioning	
Among the high-risk group, those who did not develop psychosis reported a medium-sized effect of better functioning than those who did; 10 studies, N = 654, *g* = 0.43, 95%CI 0.17 to 0.68, *p* = 0.001, I^2 = 54.9%, *p* = 0.018 Meta-regressions revealed a significant correlation with later publication year and lower functioning, but no association with length of follow-up, sex or age. Authors report no publication bias.	
Consistency in results	Inconsistent
Precision in results	Precise
Directness of results	Direct

Fusar-Poli P, Cappucciati M, Borgwardt S, Woods SW, Addington J, Nelson B, Nieman DH, Stahl DR, Rutigliano G, Riecher-Rössler A, Simon AE, Mizuno M, Lee TY, Kwon JS, Lam MML, Perez J, Keri S, Amminger P, Metzler S, Kawohl W, Rössler W, Lee J, Labad J, Ziermans T, An SK, Liu C, Woodberry KA, Braham A, Corcoran C, McGorry P, Yung AR, McGuire PK

Heterogeneity of Psychosis Risk Within Individuals at Clinical High Risk. A Meta-analytical Stratification

JAMA Psychiatry 2016; 73(2): 113-120

View review abstract online

Comparison	**Rates of transition to psychosis in people meeting clinical high risk for psychosis criteria according to; brief limited intermittent psychotic symptoms (BLIPS) vs. attenuated psychotic symptoms (APS) vs. genetic risk and deterioration syndrome (GRD) vs. no clinical risk (CHR-).**
Summary of evidence	**Moderate quality evidence (large samples, unable to assess consistency, some imprecision, direct) suggests people meeting BLIPS criteria had higher transition rates by ≥ 48 months than people meeting APS criteria, who had higher transition rates than people meeting GPD criteria, who had similar transition rates to people at no clinical risk.**

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Transition to psychosis
At 6 months, BLIPS and APS had higher transition rates than GPD and CHR- ($p < 0.001$);
BLIPS: 19 studies, N = 219, mean prevalence = 0.10, 95%CI 0.02 to 0.20
APS: 19 studies, N = 1839, mean prevalence = 0.10, 95%CI 0.08 to 0.13
GRD: 19 studies, N = 154, mean prevalence = 0.0, 95%CI 0.0 to 0.01
CHR−: 8 studies, N = 1021, mean prevalence = 0.0, 95%CI 0.0 to 0.02
At 12 months, BLIPS had higher transition rates than APS, which had higher transition rates than GPD and CHR- ($p < 0.001$);
BLIPS: 24 studies, N = 294, mean prevalence = 0.22, 95%CI 0.14 to 0.32
APS: 24 studies, N = 2093, mean prevalence = 0.16, 95%CI 0.13 to 0.19
GRD: 24 studies, N = 161, mean prevalence = 0.01, 95%CI 0.0 to 0.05
CHR−: 7 studies, N = 879, mean prevalence = 0.0, 95%CI 0.0 to 0.01
At 24 months, BLIPS had higher transition rates than APS, which had higher transition rates than GPD and CHR- ($p < 0.001$);
BLIPS: 22 studies, N = 285, mean prevalence = 0.39, 95%CI 0.7 to 0.51
APS: 22 studies, N = 2694, mean prevalence = 0.19, 95%CI 0.15 to 0.23
GRD: 22 studies, N = 196, mean prevalence = 0.03, 95%CI 0.0 to 0.08
CHR−: 8 studies, N = 1052, mean prevalence = 0.01, 95%CI 0.0 to 0.03
At 36 months, BLIPS had higher transition rates than APS, which had higher transition rates than GPD and CHR- ($p < 0.001$);
BLIPS: 12 studies, N = 180, mean prevalence = 0.38, 95%CI 0.26 to 0.49
APS: 12 studies, N = 1533, mean prevalence = 0.21, 95%CI 0.16 to 0.25
GRD: 12 studies, N = 122, mean prevalence = 0.05, 95%CI 0.0 to 0.12
CHR−: 7 studies, N = 863, mean prevalence = 0.01, 95%CI 0.0 to 0.05
At ≥48 months, BLIPS had higher transition rates than APS, which had higher transition rates than GPD and CHR- ($p < 0.001$);
BLIPS: 6 studies, N = 137, mean prevalence = 0.38, 95%CI 0.28 to 0.48
APS: 6 studies, N = 734, mean prevalence = 0.24, 95%CI 0.21 to 0.27
GRD: 6 studies, N = 64, mean prevalence = 0.08, 95%CI 0.0 to 0.19
CHR−: 3 studies, N = 134, mean prevalence = 0.04, 95%CI 0.0 to 0.13
Meta-regressions showed a significant effect for publication year on risk of psychosis onset at 24 months, with the most recent studies reporting a lower risk than the oldest studies. A higher proportion of antipsychotic agent exposure was associated with an increased risk of psychosis at 36 months. There were not association with age, sex, baseline functioning, duration of untreated

attenuated psychotic symptoms, diagnostic criteria, and study quality. There was no evidence of publication bias.	
Consistency in results	Unable to assess; no measure of consistency is reported.
Precision in results	Some imprecision.
Directness of results	Direct

Fusar-Poli P, Cappucciati M, Bonoldi I, Hui LMC, Rutigliano G, Stahl DR, Borgwardt S, Politi P, Mishara AL, Lawrie SM, Carpenter WT, McGuire PK

Prognosis of Brief Psychotic Episodes. A Meta-analysis

JAMA Psychiatry 2016; 73(3): 211-220

View review abstract online

Comparison	**Risk of psychotic recurrence in people with first-episode psychosis (FEP) vs. people with acute and transient psychotic disorder (ATPD) vs. people with brief psychotic disorder (BPD) vs. people with brief intermittent psychotic symptoms (BIPS) vs. people with brief limited intermittent psychotic symptoms (BLIPS).**
Summary of evidence	**Moderate quality evidence (large samples, unable to assess consistency, some imprecision, direct) suggests the risk of psychotic recurrence was significantly higher in the FES group compared with the other 4 groups by ≥ 36 months.**

Risk of psychotic recurrence

There were no differences in the risk of psychotic recurrence between ATPD, BPD, BLIPS, and BIPS groups at any follow-up period, but the risk of psychotic recurrence was significantly higher in the FES group compared with the other 4 groups at 24 months and 36 months only;

6 months, 25 studies, N = 1311

Brief limited intermittent psychotic symptoms (BLIPS): prevalence = 0.08, 95%CI 0.00 to 0.23

Brief intermittent psychotic symptoms (BIPS): prevalence = 0.22, 95%CI 0.09 to 0.36

Acute and transient psychotic disorder (ATPD): prevalence = 0.13, 95%CI 0.09 to 0.18

Brief psychotic disorder (BPD): prevalence = 0.20, 95%CI 0.08 to 0.36

First-episode psychosis (FES): prevalence = 0.30, 95%CI 0.15 to 0.48

BLIPS vs. BIPS vs. ATPD vs. BPD: Q = 4.71, *p* = 0.19 BLIPS vs. BIPS vs. ATPD vs. BPD vs. FES: Q = 7.63, *p* = 0.11 12 months, 46 studies, N = 1883 Brief limited intermittent psychotic symptoms (BLIPS): prevalence = 0.28, 95%CI 0.08 to 0.52 Brief intermittent psychotic symptoms (BIPS): prevalence = 0.35, 95%CI 0.23 to 0.48 Acute and transient psychotic disorder (ATPD): prevalence = 0.30, 95%CI 0.19 to 0.42 Brief psychotic disorder (BPD): prevalence = 0.31, 95%CI 0.12 to 0.52 First-episode psychosis (FES): prevalence = 0.42, 95%CI 0.30 to 0.54 BLIPS vs BIPS vs ATPD vs BPD: Q = 0.90, *p* = 0.83 BLIPS vs. BIPS vs ATPD vs BPD vs FES: Q = 2.36, *p* = 0 .67 24 months 35 studies, N = 1669 Brief limited intermittent psychotic symptoms (BLIPS): prevalence = 0.32, 95%CI 0.11 to 0.57 Brief intermittent psychotic symptoms (BIPS): prevalence = 0.43, 95%CI 0.26 to 0.61 Acute and transient psychotic disorder (ATPD): prevalence = 0.38, 95%CI 0.27 to 0.48 Brief psychotic disorder (BPD): prevalence = 0.46, 95%CI 0.31 to 0.60 First-episode psychosis (FES): prevalence = 0.78, 95%CI 0.58 to 0.93 BLIPS vs BIPS vs ATPD vs BPD: Q = 1.20, *p* = 0.75 BLIPS vs. BIPS vs ATPD vs BPD vs FES: 11.97, *p* = 0.02 ≥36 months, 42 studies, N = 11,133 Brief limited intermittent psychotic symptoms (BLIPS): prevalence = 0.30, 95%CI 0.12 to 0.52 Brief intermittent psychotic symptoms (BIPS): prevalence = 0.46, 95%CI 0.32 to 0.61 Acute and transient psychotic disorder (ATPD): prevalence = 0.54, 95%CI 0.41 to 0.66 Brief psychotic disorder (BPD): prevalence = 0.53, 95%CI 0.34 to 0.72 First-episode psychosis (FES): prevalence = 0.84, 95%CI 0.70 to 0.94 BLIPS vs. BIPS vs. ATPD vs. BPD: Q = 3.65, *p* = 0.30 BLIPS vs. BIPS vs ATPD vs BPD vs FES: Q = 16.97, *p* < 0.001 Male sex and discontinued antipsychotic use increased the estimates. There were no modulating effects of year of publication, age, diagnostic criteria used to assess the brief psychotic episode at follow-up, and study quality. There were no differences affective between ATPD, BPD, BLIPS and BIPS groups in the risk of developing schizophrenia. There was no publication bias.	
Consistency in results	Unable to assess; no measure of consistency is reported.

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Precision in results	Some imprecision.
Directness of results	Direct

Jordan G, MacDonald K, Pope MA, Schorr E, Malla AK, Iyer SN

Positive changes experienced after a first episode of psychosis: A systematic review

Psychiatric Services 2018; 69: 84-99

View review abstract online

Comparison	**Positive outcomes after a first episode of psychosis.**
Summary of evidence	**Moderate quality evidence (large sample, unable to assess consistency or precision, direct) suggests there are positive outcomes after a first-episode of psychosis for the patient, their family and their friends involving more insight and clarity, improved relationships, and greater religiosity.**
Positive outcomes	
40 studies, N = 715 Authors report that after a first-episode of psychosis, patients, their families and friends find positive changes at the individual level (e.g., insight and clarity), at the interpersonal level (e.g., improved relationships), and at spiritual levels (e.g., greater religiosity). These changes were enabled by medical, personal, family and friend support. The individual studies consisted of small samples and only half of the studies met ≥50% of the study quality criteria.	
Consistency in results	Unable to assess; no measure of consistency is reported.
Precision in results	Unable to assess; no measure of precision is reported.
Directness of results	Direct

McGinty J, Upthegrove R

Depressive symptoms during first episode psychosis and functional

outcome: A systematic review and meta-analysis **Schizophrenia Research 2020; 218: 14-27** View review abstract online	
Comparison	**Depressive symptoms and functional outcome after a first episode of psychosis.**
Summary of evidence	**High quality evidence (large sample, consistent, precise, direct) suggests more severe depressive symptoms during a first episode psychosis were weakly correlated with poorer functioning at follow-up (12-24 months).**
Functioning	
Increased depressive symptoms during a first episode psychosis were weakly correlated with poorer functioning at follow-up (12-24 months); 7 studies, N = 932, r = -0.16, 95%CI -0.24 to -0.09, $p < 0.001$, I^2 = 23%, p = 0.26 There was no moderating effect of length of follow-up. *There was no association with functional remission rates (1-10 years);* 9 studies, N = 2,265, OR = 0.87, 95%CI 0.68 to 1.13, p = 0.294, I^2 = 66%, p = 0.003 There was no moderating effect of remission definitions.	
Consistency in results	Consistent for functioning, inconsistent for remission.
Precision in results	Precise
Directness of results	Direct

Menezes NM, Arenovich T, Zipursky R **A systematic review of longitudinal outcome studies of first-episode psychosis** **Psychological Medicine 2006; 36(10): 1349-1362.** View review abstract online	
Comparison	**Longitudinal outcomes of people with a first episode of psychosis.**

Summary of evidence	**Moderate quality evidence (large sample, direct, unable to assess consistency or precision) suggests most people with a first episode psychosis have good or intermediate outcomes over 2 to 3 years from onset. Predictors of good outcome include a combination of pharmacotherapy and psychosocial therapy, and being from a developing country. Predictors of a worse outcome include being treatment naïve at study entry, and being medicated with first generation antipsychotics alone, compared to second generation antipsychotics alone or a combination of both.**
Overall outcomes of readmission, relapse, employment, and functioning	
Thirty-seven studies were included (N = 4,100) Good outcome = 42% of the population Intermediate outcome = 35% of the population Poor outcome = 27% of the population	
Predictors associated with outcome	
Significant predictors of better outcome; A combination of pharmacotherapy and psychosocial therapy: F = 4.29, $p = 0.05$ Being from a developing country: F = 12.66, $p < 0.01$ *Significant predictors of worse outcome;* Being treatment-naïve at study entry: F = 10.78, $p < 0.01$ Use of first generation 'typical' antipsychotics alone compared to second generation 'atypical' antipsychotics alone or a combination of antipsychotics: F = 16.68, $p < 0.01$	
Specific outcomes *Employment* Combination therapy (F = 6.55, $p = 0.03$) and a non-representative sample (F = 9.81, $p = 0.01$) were associated with higher rates of employment/education at follow up. *Global Function* Being treatment naïve at onset (F = 21.70, $p < 0.01$) was associated with better global functioning at follow up (measured by GAF scale), although being treatment naïve at onset was associated with worse overall outcomes.	
Consistency in results	Unable to assess; no measure of consistency is reported.

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Precision in results	Unable to assess; no measure of precision is reported.
Directness of results	Direct

Mullin K, Gupta P, Compton MT, Nielssen O, Harris A, Large M

Does giving up substance use work for patients with psychosis? A systematic meta-analysis

Australian and New Zealand Journal of Psychiatry 2012; 0: 1-14

View review abstract online

Comparison	**Symptoms and outcomes in people with first-episode schizophrenia with comorbid SUD vs. non-first-episode schizophrenia with former SUD.**
Summary of evidence	**Moderate to high quality evidence (large sample, mostly consistent, precise, direct) suggests a significant small effect that people with first-episode schizophrenia with current SUD show worse positive and depressive symptoms, and worse global functioning compared to people with first-episode schizophrenia with former SUD. No differences were reported in negative symptoms, and no differences were reported in subgroup analysis comparing first-episode studies to chronic schizophrenia studies.**

Symptoms and functioning

23 studies, N = 1,565

A significant small effect suggests that people with first-episode schizophrenia with current SUD showed worse positive and depressive symptoms, and worse global functioning compared to people with first-episode schizophrenia with former SUD. No differences were reported in negative symptoms, and no differences were reported in effect sizes between first-episode patients and chronic schizophrenia patients.

Positive symptoms;

First-episode schizophrenia: 9 studies, $d = 0.36$, 95%CI 0.14 to 0.58, $p = 0.001$, $I^2 = 41.6$

Chronic schizophrenia: 8 studies, $d = 0.20$, 95%CI -0.06 to 0.45, $p = 0.13$, $I^2 = 32.3$

$Q_B = 0.85$, $p = 0.36$

Depressive symptoms; First-episode schizophrenia: 5 studies, *d* = 0.52, 95%CI 0.13 to 0.92, *p* = 0.01, I^2 = 79.0 Chronic schizophrenia: 6 studies, *d* = 0.25, 95%CI -0.12 to 0.62, *p* = 0.19, I^2 = 0.0 Q_B = 1.0, *p* = 0.31 *Global functioning;* First-episode schizophrenia: 6 studies, *d* = -0.41, 95%CI -0.66 to -0.15, *p* = 0.002, I^2 = 25.8 Chronic schizophrenia: 3 studies, *d* = 0.04, 95%CI -0.34 to 0.43, *p* = 0.83, I^2 = 25.1 Q_B = 3.62, *p* = 0.06 *Negative symptoms;* First-episode schizophrenia: 8 studies, *d* = 0.22, 95%CI -0.03 to 0.47, *p* = 0.08, I^2 = 0.0 Chronic schizophrenia: 4 studies, *d* = 0.10, 95%CI -0.22 to 0.42, *p* = 0.55, I^2 = 70.1 Q_B = 0.83, *p* = 0.36	
Consistency in results	Authors report high inconsistency for first-episode depressive symptoms and chronic schizophrenia negative symptoms (*p* values not reported, I^2 > 50%).
Precision in results	Precise
Directness of results	Direct

Simon AE, Velthorst E, Nieman DH, Linszen D, Umbricht D, de Haan L

Ultra high-risk state for psychosis and non-transition: A systematic review

Schizophrenia Research 2011; 132: 8-17

View review abstract online

Comparison	**Transition to psychosis in people at clinical high risk.**
Summary of evidence	**Moderate quality evidence (large sample, unable to assess consistency or precision, direct) indicates the mean risk of transition to full psychotic episode in clinical high risk groups is 24%. An older mean age at baseline was associated with significantly lower transition rates in studies with longer follow-up (>1 year). More recent publications reported lower transition rates than older publications, but only those with naturalistic**

	designs (no interventions included).
Transition to psychotic episode	
31 studies, N = 3,539 The mean transition risk to a full psychotic episode from a clinical high risk state was 24% (SD 12.1%). An older mean age at baseline was associated with significantly lower transition rates in studies with longer follow-up (> 1 year), (adjusted R^2 = 0.28, p = 0.02), but in studies of any duration there was no association found with age. Lower transition rates were associated with more recent publications (non-adjusted R^2 = 0.18, p = 0.02), particularly in naturalistic studies (adjusted R^2 = 0.27, p = 0.02). A relationship with year was not found for intervention studies (adjusted R^2 = 0.18, p = 0.19).	
Consistency in results	Unable to assess; no measure of consistency is reported.
Precision in results	Unable to assess; no measure of precision is reported.
Directness of results	Direct

Explanation of acronyms

BPRS = Brief Psychiatric Rating Scale, CATEGO-DHA = computer based diagnostic program based on the Present State Examination (PSE), CGI = Clinical Global Impression Scale, CI = Confidence Interval, DAS-M = Social Disability (WHO, 1988), F = statistic difference between groups in multivariate analyses, FEP = First Episode Psychosis, GAF = Global Assessment of Function scale, LCS = Life Chart Scale, MADRS = Montgomery-Asberg Depression Rating Scale, N = number of participants, p = statistical probability of obtaining that result ($p < 0.05$ generally regarded as significant), PANSS = Positive and Negative Symptom Scale, PSE = Present State Examination, QLS = Quality of Life Scale, SANS = Scale for Assessment of Negative Symptoms, SAPS = Scale for Assessment of Positive Symptoms, SOFAS = Social and Occupational Functioning Assessment Scale, SUD = Substance Use Disorder

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Explanation of technical terms

* Bias has the potential to affect reviews of both RCT and observational studies. Forms of bias include; reporting bias – selective reporting of results; publication bias - trials that are not formally published tend to show less effect than published trials, further if there are statistically significant differences between groups in a trial, these trial results tend to get published before those of trials without significant differences; language bias – only including English language reports; funding bias - source of funding for the primary research with selective reporting of results within primary studies; outcome variable selection bias; database bias - including reports from some databases and not others; citation bias - preferential citation of authors. Trials can also be subject to bias when evaluators are not blind to treatment condition and selection bias of participants if trial samples are small[15].

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† Different effect measures are reported by different reviews.

Prevalence refers to how many existing cases there are at a particular point in time. Incidence refers to how many new cases there are per population in a specified time period. Incidence is usually reported as the number of new cases per 100,000 people per year. Alternatively some studies present the number of new cases that have accumulated over several years against a person-years denominator. This denominator is the sum of individual units of time that the persons in the population are at risk of becoming a case. It takes into account the size of the underlying population sample and its age structure over the duration of observation.

Reliability and validity refers to how accurate the instrument is. Sensitivity is the proportion of actual positives that are correctly identified (100% sensitivity = correct identification of all actual positives) and specificity is the proportion of negatives that are correctly identified (100% specificity = not identifying anyone as positive if they are truly not).

Weighted mean difference scores refer to mean differences between treatment and comparison groups after treatment (or occasionally pre to post treatment) and in a randomised trial there is an assumption that both groups are comparable on this measure prior to treatment. Standardised mean differences are divided by the pooled standard deviation (or the standard deviation of one group when groups are homogenous) which allows results from different scales to be combined and compared. Each study's mean difference is then given a weighting depending on the size of the sample and the variability in the data. 0.2 represents a small effect, 0.5 a medium effect, and 0.8 and over represents a large effect[15].

Odds ratio (OR) or relative risk (RR) refers to the probability of a reduction (< 1) or an increase (> 1) in a particular outcome in a treatment group, or a group exposed to a risk factor, relative to the comparison group. For example, a RR of 0.75 translates to a reduction in risk of an outcome of 25% relative to those not receiving the treatment or not exposed to the risk factor. Conversely, a RR of 1.25 translates to an increased risk of 25% relative to those not receiving treatment or not having been exposed to a risk factor. A RR or OR of 1.00 means there is no difference between groups. A medium effect is considered if RR > 2 or < 0.5 and a large effect if RR > 5 or < 0.2[16]. lnOR stands for logarithmic OR where a lnOR of 0 shows no difference between groups. Hazard ratios measure the effect of an explanatory variable on the hazard or risk of an event.

Correlation coefficients (eg, r) indicate the strength of association or relationship

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between variables. They are an indication of prediction, but do not confirm causality due to possible and often unforseen confounding variables. An r of 0.10 represents a weak association, 0.25 a medium association and 0.40 and over represents a strong association. Unstandardised (*b*) regression coefficients indicate the average change in the dependent variable associated with a 1 unit change in the independent variable, statistically controlling for the other independent variables. Standardised regression coefficients represent the change being in units of standard deviations to allow comparison across different scales.

‡ Inconsistency refers to differing estimates of effect across studies (i.e. heterogeneity or variability in results) that is not explained by subgroup analyses and therefore reduces confidence in the effect estimate. I^2 is the percentage of the variability in effect estimates that is due to heterogeneity rather than sampling error (chance) - 0% to 40%: heterogeneity might not be important, 30% to 60%: may represent moderate heterogeneity, 50% to 90%: may represent considerable heterogeneity and over this is considerable heterogeneity. I^2 can be calculated from Q (chi-square) for the test of heterogeneity with the following formula[15];

$$I^2 = \left(\frac{Q - df}{Q}\right) \times 100\%$$

§ Imprecision refers to wide confidence intervals indicating a lack of confidence in the effect estimate. Based on GRADE recommendations, a result for continuous data (standardised mean differences, not weighted mean differences) is considered imprecise if the upper or lower confidence limit crosses an effect size of 0.5 in either direction, and for binary and correlation data, an effect size of 0.25. GRADE also recommends downgrading the evidence when sample size is smaller than 300 (for binary data) and 400 (for continuous data), although for some topics, these criteria should be relaxed[17].

‖ Indirectness of comparison occurs when a comparison of intervention A versus B is not available but A was compared with C and B was compared with C that allows indirect comparisons of the magnitude of effect of A versus B. Indirectness of population, comparator and/or outcome can also occur when the available evidence regarding a particular population, intervention, comparator, or outcome is not available and is therefore inferred from available evidence. These inferred treatment effect sizes are of lower quality than those gained from head-to-head comparisons of A and B.

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References

1. Moher D, Liberati A, Tetzlaff J, Altman DG, PRISMAGroup (2009): Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *British Medical Journal* 151: 264-9.
2. GRADEWorkingGroup (2004): Grading quality of evidence and strength of recommendations. *British Medical Journal* 328: 1490.
3. Menezes NM, Arenovich T, Zipursky RB (2006): A systematic review of longitudinal outcome studies of first-episode psychosis. *Psychological Medicine* 36: 1349-62.
4. Archie S, Gyomorey K (2009): First episode psychosis, substance abuse and prognosis: A systematic review. *Current Psychiatry Reviews* 5: 153-63.
5. Mullin K, Gupta P, Compton MT, Nielssen O, Harris A, Large M (2012): Does giving up substance use work for patients with psychosis? A systematic meta-analysis. *Australian and New Zealand Journal of Psychiatry* 46: 826-39.
6. Allott K, Liu P, Proffitt TM, Killackey E (2011): Cognition at illness onset as a predictor of later functional outcome in early psychosis: Systematic review and methodological critique. *Schizophrenia Research* 125: 221-35.
7. Simon AE, Velthorst E, Nieman DH, Linszen D, Umbricht D, de Haan L (2011): Ultra high-risk state for psychosis and non-transition: a systematic review. *Schizophrenia Research* 132: 8-17.
8. Cotter J, Drake RJ, Bucci S, Firth J, Edge D, Yung AR (2014): What drives poor functioning in the at-risk mental state? A systematic review. *Schizophrenia Research* 159: 267-77.
9. Fusar-Poli P, Rocchetti M, Sardella A, Avila A, Brandizzi M, Caverzasi E*, et al.* (2015): Disorder, not just state of risk: Meta-analysis of functioning and quality of life in people at high risk of psychosis. *British Journal of Psychiatry* 207: 198-206.
10. Fusar-Poli P, Cappucciati M, Bonoldi I, Hui LMC, Rutigliano G, Stahl DR*, et al.* (2016): Prognosis of brief psychotic episodes a meta-analysis. *JAMA Psychiatry* 73: 211-20.
11. Fusar-Poli P, Cappucciati M, Borgwardt S, Woods SW, Addington J, Nelson B*, et al.* (2016): Heterogeneity of psychosis risk within individuals at clinical high risk: A meta-analytical stratification. *JAMA Psychiatry* 73: 113-20.
12. Fusar-Poli P, Bonoldi I, Yung AR, Borgwardt S, Kempton MJ, Valmaggia L*, et al.* (2012): Predicting psychosis: meta-analysis of transition outcomes in individuals at high clinical risk. *Archives of General Psychiatry* 69: 220-9.
13. Jordan G, MacDonald K, Pope MA, Schorr E, Malla AK, Iyer SN (2018): Positive changes experienced after a first episode of psychosis: A systematic review. *Psychiatric Services* 69: 84-99.
14. McGinty J, Upthegrove R (2020): Depressive symptoms during first episode psychosis and functional outcome: A systematic review and meta-analysis. *Schizophrenia Research* Jan: doi: 10.1016/j.schres.2019.12.011.
15. CochraneCollaboration (2008): Cochrane Handbook for Systematic Reviews of Interventions. Accessed 24/06/2011.
16. Rosenthal JA (1996): Qualitative Descriptors of Strength of Association and Effect Size. *Journal of Social Service Research* 21: 37-59.
17. GRADEpro (2008): [Computer program]. Jan Brozek, Andrew Oxman, Holger Schünemann. *Version 32 for Windows*