TECHNICAL COMMENTARY

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Cognition in high-risk groups

Introduction

There are two key approaches for identifying people with early signs that may suggest a high risk of developing psychosis or schizophrenia. The first approach is based on Huber's Basic Symptoms that focuses on a detailed way of describing phenomenological (subjective) disturbances. Because the basic symptoms refer only to subtle subjectively experienced abnormalities, they may reflect an earlier phase in the disease process than the second approach, which identifies at risk mental states as a combination of: a family history of psychosis (familial risk) plus non-specific symptoms and recent decline in functioning; recent onset Attenuated Psychotic Symptoms with decline in functioning; and Brief Limited Intermittent Psychotic Symptoms.

Cognitive deficits are common in people with schizophrenia and may also be apparent in people at high risk of psychosis. This table presents the available evidence for cognitive performance in this group of people.

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 early signs or symptoms of first episode psychosis or 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 seven systematic reviews that met our inclusion criteria[3-9].

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- High quality evidence shows small to medium-sized effects of poorer general intelligence, executive functioning, attention, visual memory, and social cognition in people at high risk of psychosis compared to controls. Moderate to high quality evidence also suggests poorer visual-spatial ability, olfactory functioning, verbal fluency, verbal memory, working memory, learning, processing speed and reasoning.
- High quality evidence suggests people at clinical high risk of psychosis and familial high risk of psychosis are similarly impaired on processing speed, verbal and visual memory, attention and language fluency when compared with controls. People at familial high risk were more impaired on premorbid and current IQ than those at clinical high risk, and those at clinical high risk were more impaired on visuospatial working memory than those at familial high risk.
- Moderate to high quality evidence found large effects of poorer speed of processing and poorer verbal learning in people at high risk of psychosis who converted to psychosis when compared to controls. There were also medium to large effects of poorer visual learning, working memory and IQ, and medium-sized effects of poorer attention and reasoning in converters. Moderate quality evidence found converters also showed medium-sized effects of poorer olfactory functioning, language functioning, visual-spatial ability, and executive functioning. In non-converters, there were medium-sized effects of poorer verbal learning and current IQ, and small effects of poorer attention, reasoning, speed of processing and premorbid IQ. There were no differences in visual learning and working memory in non-converters.
- Compared to people with first-episode psychosis, moderate to high quality evidence shows medium-sized effects of better attention, verbal learning, and working memory, and small effects of better current IQ and speed of processing in people at clinical high-risk of psychosis.

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Bora E, Lin A, Wood SJ, Yung AR, McGorry PD, Pantelis C

Cognitive deficits in youth with familial and clinical high risk to psychosis: A systematic review and meta-analysis

Acta Psychiatrica Scandinavica 2014; 130(1): 1-15

View review abstract online

Comparison	**Cognitive functioning in people at clinical high risk (UHR) and familial high risk (FHR) for psychosis vs. controls.**
Summary of evidence	**High quality evidence (large samples, consistent, precise, direct) suggests people at clinical high risk of psychosis and familial high risk of psychosis are similarly impaired on processing speed, verbal and visual memory, attention and language fluency when compared with controls, showing small to medium sized effects. Moderate to high quality evidence (indirect) finds people at familial high risk were more impaired on premorbid and current IQ than those at clinical high risk, and those at clinical high risk were more impaired on visuospatial working memory.**

Cognitive functioning

*Significant, small to medium size effect of **poorer premorbid IQ** in UHR and FHR groups compared with controls, with the FHR group showing the greatest deficit;*

UHR: 9 studies, N = 1,370, d = 0.30, 95%CI 0.13 to 0.48, $p < 0.001$, I^2 = 0.04%, Q-test p = 0.02

FHR: 6 studies, N = 770, d = 0.63, 95%CI 0.47 to 0.79, $p < 0.001$, I^2 = 0%, Q-test p = 0.60

Q_B = 13.1, $p < 0.001$

*Significant, medium to large size effect of **poorer current IQ** in UHR and FHR groups compared with controls, with the FHR group showing the greatest deficit;*

UHR: 12 studies, N = 1,440, d = 0.40, 95%CI 0.25 to 0.54, $p < 0.001$, I^2 = 0.02%, Q-test p = 0.15

FHR: 8 studies, N = 900, d = 0.81, 95%CI 0.61 to 1.01, $p < 0.001$, I^2 = 0.04%, Q-test p = 0.07

Q_B = 20.0, $p < 0.001$

*Significant, small to medium size effect of **poorer visuospatial working memory** in UHR and FHR groups compared with controls, with the UHR group showing the greatest deficit;*

UHR: 9 studies, N = 802, d = 0.71, 95%CI 0.39 to 1.04, $p < 0.001$, I^2 = 0.18%, Q-test $p < 0.001$

FHR: 4 studies, N = 426, d = 0.35, 95%CI 0.01 to 0.71, p = 0.04, I^2 = 0.09%, Q-test p = 0.02

Q_B = 4.6, p = 0.03

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*Significant, small to medium size effect of **poorer processing speed** in UHR and FHR groups compared with controls, with no significant differences between groups;*

UHR: 8 studies, N = 974, d = 0.47, 95%CI 0.27 to 0.66, $p < 0.001$, I^2 = 0.04%, Q-test p = 0.04

FHR: 13 studies, N = 1,494, d = 0.35, 95%CI 0.22 to 0.49, $p < 0.001$, I^2 = 0.02%, Q-test p = 0.13

Q_B $p > 0.05$

*Significant, medium size effect of **poorer verbal memory** in UHR and FHR groups compared with controls, with no significant differences between groups;*

UHR: 10 studies, N = 1,205, d = 0.50, 95%CI 0.32 to 0.68, $p < 0.001$, I^2 = 0.04%, Q-test p = 0.03

FHR: 12 studies, N = 1,547, d = 0.45, 95%CI 0.29 to 0.61, $p < 0.001$, I^2 = 0.03%, Q-test p = 0.06

Q_B $p > 0.05$

*Significant, medium size effect of **poorer visual memory** in UHR and FHR groups compared with controls, with no significant differences between groups;*

UHR: 8 studies, N = 955, d = 0.50, 95%CI 0.23 to 0.77, p = 0.0002, I^2 = 0.10%, Q-test p = 0.001

FHR: 8 studies, N = 985, d = 0.51, 95%CI 0.30 to 0.72, $p < 0.001$, I^2 = 0.04%, Q-test p = 0.08

Q_B $p > 0.05$

*Significant, small to medium size effect of **poorer verbal working memory** in UHR and FHR groups compared with controls, with no significant differences between groups;*

UHR: 9 studies, N = 1,136, d = 0.41, 95%CI 0.20 to 0.61, $p < 0.001$, I^2 = 0.06%, Q-test p = 0.007

FHR: 10 studies, N = 1,206, d = 0.32, 95%CI 0.12 to 0.51, p = 0.001, I^2 = 0.05%, Q-test p = 0.02

Q_B $p > 0.05$

*Significant, small size effect of **poorer attention** in UHR and FHR groups compared with controls, with no significant differences between groups;*

UHR: 8 studies, N = 1,042, d = 0.37, 95%CI 0.25 to 0.50, $p < 0.001$, I^2 = 0%, Q-test p = 0.59

FHR: 14 studies, N = 1451, d = 0.30, 95%CI 0.16 to 0.44, $p < 0.001$, I^2 = 0.03%, Q-test p = 0.08

Q_B $p > 0.05$

*Significant, small to medium size effect of **poorer language fluency** in UHR and FHR groups compared with controls, with no significant differences between groups;*

UHR: 8 studies, N = 930, d = 0.52, 95%CI 0.30 to 0.74, $p < 0.001$, I^2 = 0.06%, Q-test p = 0.01

FHR: 10 studies, N = 1,149, d = 0.39, 95%CI 0.16 to 0.61, p = 0.001, I^2 = 0.08%, Q-test p = 0.002

Q_B $p > 0.05$

Meta-regression of the UHR studies showed that increased deterioration in functioning was associated with more severe deficits in verbal memory, premorbid IQ and attention. In FHR studies, symptomatic subjects were significantly more impaired than asymptomatic subjects in the two domains examined: verbal memory and processing speed. Lower transition to psychosis rate was significantly associated with higher IQ.

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Authors report no publication bias.	
Consistency‡	Consistent
Precision§	Precise
Directness‖	Direct in comparisons with controls, indirect in comparisons between high-risk groups.

Bora E, Murray RM

Meta-analysis of cognitive deficits in ultra-high risk to psychosis and first-episode psychosis: Do the cognitive deficits progress over, or after, the onset of psychosis?

Schizophrenia Bulletin 2014; 40(43): 744-755

View review abstract online

Comparison	**Changes in cognitive functioning over time in people at ultra-high risk of psychosis (UHR) vs. people with first-episode psychosis (FEP) or controls.**
Summary of evidence	**High quality evidence (medium to large samples, consistent, precise, direct) suggests small improvements in cognitive domains over time in people at ultra-high risk of psychosis, people with first-episode psychosis and controls. Controls showed superior performance on verbal working memory and language fluency tasks.**

Cognitive functioning over time (1 to 5 years)

*Significant, small improvement in **verbal working memory** over time in UHR and controls, with no improvement in FEP. Controls showed significantly more improvement;*

FEP: 10 studies, N = 503, d = 0.13, 95%CI -0.03 to 0.28, p = 0.10, I^2 = 0.02%, Q-test p = 0.20

UHR: 8 studies, N = 224, d = 0.20, 95%CI 0.01 to 0.39, p = 0.04, I^2 = 0%, Q-test p = 0.97

Controls: 7 studies, N = 268, d = 0.34, 95%CI 0.16 to 0.51, p < 0.001, I^2 = 0%, Q-test p = 0.79

Q_B = 4.10, p = 0.04

*Significant, small improvement in **language fluency** over time in FEP and controls, with no improvement in UHR. Controls showed significantly more improvement;*

FEP: 12 studies, N = 575, d = 0.14, 95%CI 0.01 to 0.27, p = 0.04, I^2 = 0.02%, Q-test p = 0.15

UHR: 10 studies, N = 235, *d* = 0.03, 95%CI -0.15 to 0.20, *p* = 0.76, I^2 = 0%, Q-test *p* = 0.97

Controls: 9 studies, N = 364, *d* = 0.31, 95%CI 0.14 to 0.49, *p* < 0.001, I^2 = 0.02%, Q-test *p* = 0.23

Q_B = 4.9, *p* = 0.03

*Significant, small improvement in **global cognition** over time in UHR, FEP and controls, with no significant differences between groups;*

FEP: 17 studies, N = 905, *d* = 0.30, 95%CI 0.20 to 0.39, *p* < 0.001, I^2 = 0%, Q-test *p* = 0.54

UHR: 14 studies, N = 560, *d* = 0.23, 95%CI 0.11 to 0.35, *p* < 0.001, I^2 = 0%, Q-test *p* = 0.95

Controls: 11 studies, N = 405, *d* = 0.38, 95%CI 0.24 to 0.52, *p* < 0.001, I^2 = 0%, Q-test *p* = 0.94

Q_B *p* > 0.05

*Significant, small improvement in **processing speed** over time in UHR, FEP and controls, with no significant differences between groups;*

FEP: 12 studies, N = 627, *d* = 0.19, 95%CI 0.08 to 0.30, *p* < 0.001, I^2 = 0%, Q-test *p* = 0.84

UHR 9 studies, N = 242, *d* = 0.18, 95%CI 0.0 to 0.36, *p* = 0.05, I^2 = 0%, Q-test *p* = 0.64

Controls: 8 studies, N = 299, *d* = 0.38, 95%CI 0.21 to 0.54, *p* < 0.001, I^2 = 0%, Q-test *p* = 0.85

Q_B *p* > 0.05

*Significant, small improvement in **verbal memory** over time in UHR, FEP and controls, with no significant differences between groups;*

FEP: 11 studies, N = 702, *d* = 0.33, 95%CI 0.19 to 0.47, *p* < 0.001, I^2 = 0.02%, Q-test *p* = 0.14

UHR: 12 studies, N = 532, *d* = 0.31, 95%CI 0.12 to 0.51, *p* = 0.002, I^2 = 0.06%, Q-test *p* = 0.02

Controls: 10 studies, N = 338, *d* = 0.38, 95%CI 0.17 to 0.53, *p* < 0.001, I^2 = 0.02%, Q-test *p* = 0.26

Q_B *p* > 0.05

*Significant, small to medium-sized improvement in **visual memory** over time in FEP and controls, and a trend improvement for UHR groups, with no significant differences between groups;*

FEP: 10 studies, N = 574, *d* = 0.27, 95%CI 0.06 to 0.48, *p* = 0.01, I^2 = 0.07%, Q-test *p* = 0.001

UHR: 5 studies, N = 92, *d* = 0.34, 95%CI -0.02 to 0.70, *p* = 0.06, I^2 = 0.04%, Q-test *p* = 0.25

Controls: 6 studies, N = 228, *d* = 0.45, 95%CI 0.17 to 0.53, *p* = 0.002, I^2 = 0.06%, Q-test *p* = 0.06

Q_B *p* > 0.05

*Significant, small improvement in **executive functioning** over time in UHR, FEP and controls, with no significant differences between groups;*

FEP: 12 studies, N = 678, *d* = 0.38, 95%CI 0.20 to 0.56, *p* < 0.001, I^2 = 0.05%, Q-test *p* = 0.006

UHR: 5 studies, N = 208, *d* = 0.37, 95%CI 0.17 to 0.56, *p* < 0.001, I^2 = 0%, Q-test *p* = 0.99

Controls: 6 studies, N = 265, *d* = 0.39, 95%CI 0.13 to 0.65, *p* = 0.003, I^2 = 0.05%, Q-test *p* = 0.06

Q_B *p* > 0.05

*Significant, small improvement in **attention** over time in UHR, FEP and controls, with no significant*

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differences between groups; FEP: 8 studies, N = 620, *d* = 0.27, 95%CI 0.12 to 0.42, *p* < 0.001, I^2 = 0.02%, Q-test *p* = 0.14 UHR: 8 studies, N = 219, *d* = 0.33, 95%CI 0.14 to 0.52, *p* < 0.001, I^2 = 0%, Q-test *p* = 0.87 Controls: 7 studies, N = 155, *d* = 0.27, 95%CI 0.08 to 0.46, *p* = 0.006, I^2 = 0%, Q-test *p* = 0.57 Q_B *p* > 0.05 In FEP studies, a decrease in negative symptoms was significantly associated with greater improvement in executive functioning and verbal working memory, and a decrease in positive symptoms was associated with improvement of visual memory performance at follow-up. The ratio of patients taking antipsychotic medications was not significantly associated with cognitive changes over time. Authors report no publication bias	
Consistency	Consistent
Precision	Precise
Directness	Direct in comparisons with controls, indirect in comparisons between high-risk and FEP groups.

Cohen AS, Brown LA, Auster TL

Olfaction, "olfiction," and the schizophrenia-spectrum: An updated meta-analysis on identification and acuity

Schizophrenia Research 2012; 135: 152-157

View review abstract online

Comparison	**Olfactory identification and acuity in people at risk of schizophrenia – including people with self-reported schizotypal traits, people at high genetic risk, and people displaying subclinical psychotic symptoms vs. controls.**
Summary of evidence	**Moderate to high quality evidence (large sample, unable to assess consistency. precise, direct) suggests impaired olfactory identification in people at high risk of schizophrenia.**
Olfactory performance	

Overall, a small significant effect size of impaired identification, but not acuity, in people at high risk; Olfactory identification: 16 studies, N = 1,186, *d* = -0.25, 95%CI -0.47 to -0.03, *p* value not reported Olfactory acuity: 6 studies, N = 238, *d* = -0.38, 95%CI -0.70 to 0.07, *p* value not reported *No significant differences reported in subgroup of ultra-high risk studies (family history of psychosis, functional decline or subclinical psychosis);* Identification: 2 studies, N = 219, *d* = -0.67, 95%CI -4.08 to 2.75, *p* value not reported *No significant differences reported in subgroup of psychometrically determined studies (schizotypy self-report);* Identification: 5 studies, N = 450, *d* = -0.14, 95%CI -0.64 to 0.36, *p* value not reported *No significant differences reported in biological risk studies (relatives of people with schizophrenia);* Identification: 9 studies, N = 517, *d* = -0.21, 95%CI -0.53 to 0.12, *p* value not reported	
Consistency	Unable to assess; no measure of consistency is reported.
Precision	Precise apart from ultra-high risk studies
Directness	Direct

De Herdt A, Wampers M, Vancampfort D, De Hert M, Vanhees L, Demunter H, Van Bouwel L, Brunner E, Probst M

Neurocognition in clinical high risk young adults who did or did not convert to a first schizophrenic psychosis: a meta-analysis

Schizophrenia Research 2013; 149(1-2): 48-55

View review abstract online

Comparison	**Baseline cognitive functioning in people at clinical high risk for psychosis who transitioned to psychosis at follow-up compared with those who did not transition to psychosis at follow-up.**
Summary of evidence	**Moderate quality evidence (small to medium-sized samples, consistent, precise, direct) suggests small to medium effects of poor visual learning and working memory in people at clinical high risk for psychosis who transitioned to psychosis compared with people at clinical high risk for psychosis who did not transition to psychosis. Moderate to low quality evidence (inconsistent, imprecise) suggests no differences in attention, verbal learning, reasoning ability or processing speed.**

Baseline cognitive functioning	
Overall, 9 studies with 583 clinical high-risk people (195 transitioned to psychosis, 388 did not) *Significant, medium effect of **poorer visual learning** in people at clinical high risk for psychosis who transitioned to psychosis compared with those who did not transition to psychosis;* 5 studies, *g* = -0.40, 95%CI -0.68 to -0.13, *p* = 0.004, Q-test *p* = 0.733 *A trend, small effect of **poorer working memory** in people at clinical high risk for psychosis who transitioned to psychosis compared with those who did not transition to psychosis;* 7 studies, *g* = -0.27, 95%CI -0.56 to 0.02, *p* = 0.069, Q-test *p* = 0.232 *No significant differences between groups in **attention/vigilance;*** 5 studies, *g* = -0.37, 95%CI -0.81 to 0.08, *p* = 0.107, Q-test *p* = 0.009 *No significant differences between groups in **verbal learning;*** 8 studies, *g* = -0.79, 95%CI -1.82 to 0.25, *p* = 0.137, Q-test *p* < 0.0001 *No significant differences between groups in **reasoning ability;*** 8 studies, *g* = 0.39, 95%CI -0.32 to 1.1, *p* = 0.279, Q-test *p* = 0.000 *No significant differences between groups in **processing speed*** 7 studies, *g* = -0.52, 95%CI -1.21 to 0.17, *p* = 0.138, Q-test *p* < 0.0001	
Consistency	Consistent for visual learning and working memory only.
Precision	Precise for visual learning, working memory and attention/vigilance.
Directness	Direct

Fusar-Poli P, Deste G, Smieskova R, Barlati S, Yung AR, Howes O, Stieglitz R, Vita A, McGuire P, Borwardt S

Cognitive Functioning in Prodromal Psychosis

Archives of General Psychiatry 2012; 69(6): 562-571

View review abstract online

Comparison 1	**Cognitive functioning in individuals at clinical high-risk of psychosis (showing prodromal sub-clinical symptoms) vs. controls.**
Summary of evidence	**High quality evidence (large samples, consistent, precise,**

	direct) shows a small to medium reduction in general intelligence, executive functioning, attention, visual memory and social cognition in individuals at high-risk of psychosis compared with controls. Moderate to high quality evidence (inconsistent) suggests a small to medium reduction in verbal fluency, verbal memory and working memory in individuals at high-risk of psychosis compared with controls.
Cognitive functioning	
*Small effect size suggests **poorer general intelligence** in high-risk individuals vs. controls;* 11 studies, N = 1,247, *g* = -0.224, 95%CI -0.346 to -0.101, *p* < 0.001, I^2 = 14.28, *p* = 0.308 *Small effect size suggests **poorer executive functioning** in high-risk individuals vs. controls;* 9 studies, N = 1,189, *g* = -0.218, 95%CI -0.397 to -0.118, *p* = 0.005, I^2 = 25.33, *p* = 0.218 *Small effect size suggests **poorer verbal fluency** in high-risk individuals vs. controls;* 11 studies, N = 1,382, *g* = -0.308, 95%CI -0.486 to -0.130, *p* = 0.001, I^2 = 64.19, *p* = 0.002 *Small effect size suggests **poorer attention** in high-risk individuals vs. controls;* 8 studies, N = 1,150, *g* = -0.225, 95%CI -0.432 to -0.218, *p* = 0.045, I^2 = 0, *p* = 0.773 *Small to medium effect size suggests **poorer visual memory** in high-risk individuals vs. controls;* 5 studies, N = 489, *g* = -0.396, 95%CI -0.595 to -0.196, *p* <.001, I^2 = 0, *p* = 0.566 *Small to medium effect size suggests **poorer verbal memory** in high-risk individuals vs. controls;* 8 studies, N = 910, *g* = -0.392, 95%CI -0.579 to -0.206, *p* <.001, I^2 = 54.94, *p* = 0.030 *Small to medium effect size suggests **poorer working memory** in high-risk individuals vs. controls;* 11 studies, N = 1,471, *g* = -0.360, 95%CI -0.512 to -0.209, *p* <.001, I^2 = 49.93, *p* = 0.030 *Medium effect size suggests **poorer social cognition** in high-risk individuals vs. controls;* 6 studies, N = 490, *g* = -0.547, 95%CI -0.730 to -0.363, *p* <.001, I^2 = 0, *p* = 0.919 *No differences in **processing speed;*** 14 studies, N = 1,646, *g* = -0.176, 95%CI -0.176 to 0.066, *p* = 0.109, I^2 = 52.97, *p* = 0.010 Older age showed a weak relationship with worse cognitive performance in high-risk individuals vs. controls (β = −0.025, *p* < 0.001). Milder cognitive impairments were reported in studies using the Basic Symptoms approach (*g* = −0.227, *p* not reported), intermediate impairments in studies adopting the Ultra High Risk approach (*g* = −0.357), and the most pronounced impairments were reported in studies combining the two approaches (*g* = −0.410), although these group differences were not statistically significant (Q_B = 1.17, *p* = 0.56). There was a trend level significance effect of sex with females performing relatively better than males (females *g* = −0.208, males: *g* = −0.366, Q_B = 4.86, *p* = 0.053). There was no significant effect of study publication year (β = −0.015, *p* = 0.61), or exposure to antipsychotic medication (Q_B = 1.130, *p* = 0.57). Authors report that high-risk subjects were best distinguished from controls on the performance of

the Digit Symbol Substitution Test, Letter Number Sequencing task, and the Continuous Performance Test, as these tasks showed the smallest confidence intervals.	
Consistency in results	Consistent for general intelligence, executive functioning, attention, visual memory and social cognition.
Precision in results	Precise
Directness of results	Direct
Comparison 2	**Cognitive functioning in individuals at high-risk of psychosis who made the transition to psychosis compared with individuals at high-risk of psychosis who did not make the transition to psychosis (up to 19 months follow up).**
Summary of evidence	**Moderate to low quality evidence (medium-sized samples, unable to assess consistency or precision, direct) suggests a medium reduction in general intelligence, verbal fluency, verbal memory, visual memory, and working memory in high-risk individuals who made the transition to psychosis compared with high-risk individuals who did not make the transition to psychosis.**
Cognitive functioning	
7 studies, N = 598 Authors report a medium effect (*g* = -3.00 to -4.00) showing lower general intelligence, verbal fluency, verbal memory, visual memory, and working memory in high-risk individuals who made the transition to psychosis compared with high-risk individuals who did not make the transition to psychosis.	
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

Giuliano AJ, Huijun L, Mesholam-Gately R, Sorenson SM, Woodberry KA, Seidman LJ

Neurocognition in Psychosis Risk Syndrome: A Quantitative and Qualitative Review

Current Pharmaceutical Design 2012, 18: 399-415 View review abstract online	
Comparison 1	**Cognitive functioning in individuals at clinical high-risk of psychosis vs. controls.**
Summary of evidence	**Moderate to high quality evidence (unclear sample sizes, consistent, precise, direct) shows a medium reduction in olfactory functioning, executive functioning, and verbal and non-verbal memory in individuals at high-risk of psychosis compared with controls. Moderate quality evidence (inconsistent) suggests a medium reduction in general intelligence, language functioning, attention, visual-spatial ability, and delayed verbal memory and learning in individuals at high-risk of psychosis compared with controls.**
Cognitive functioning	
*Medium effect size suggests **poorer olfactory functioning** in high-risk individuals;* 2 studies, d = -0.67, 95%CI -1.06 to -0.28, $p < 0.05$, I^2 = 39%, p = 0.20 *Medium effect size suggests **poorer general cognitive ability/IQ** in high-risk individuals;* 6 studies, d = -0.53, 95%CI -0.79 to -0.26, $p < 0.05$, I^2 = 67.9%, $p < 0.01$ Moderator analysis revealed larger effect sizes in samples with higher % of males ($p < 0.02$). *Medium effect size suggests **poorer language functioning** in high-risk individuals;* 10 studies, d = -0.51, 95%CI -0.64 to -0.38, $p < 0.05$, I^2 = 57.3%, $p < 0.001$ Moderator analysis revealed larger effect sizes in older samples ($p < 0.01$), and in studies with ascertainment methods other than the Comprehensive Assessment of At-Risk Mental States (CAARMS) ($p < 0.01$). *Medium effect size suggests **poorer immediate verbal memory** in high-risk individuals;* 8 studies, d = -0.50, 95%CI -0.61 to -0.39, $p < 0.05$, I^2 = 31.6%, p = 0.07 Moderator analysis revealed larger effect sizes in studies with ascertainment methods other than the CAARMS ($p < 0.03$). *Medium effect size suggests **poorer attention-processing speed** in high-risk individuals;* 7 studies, d = -0.43, 95%CI -0.54 to -0.32, $p < 0.05$, I^2 = 48.8%, $p < 0.01$ No significant moderators. *Medium effect size suggests **poorer visual-spatial ability** in high-risk individuals;* 4 studies, d = -0.42, 95%CI -0.74 to -0.10, $p < 0.05$, I^2 = 75.6%, $p < 0.01$ Moderator analysis revealed smaller effect sizes in more recent publications ($p < 0.05$), in studies	

with a higher % of males in the patient samples ($p < 0.03$), and larger effect sizes in studies with a higher % of males in the control samples ($p < 0.03$). Larger effect sizes were also reported in studies with a higher % of patients with a familial risk of psychosis (($p < 0.03$). *Medium effect size suggests **poorer attention-vigilance** in high-risk individuals;* 8 studies, d = -0.40, 95%CI -0.50 to -0.30, $p < 0.05$, I^2 = 45.2%, $p < 0.001$ Moderator analysis revealed smaller effect sizes in more recent publications ($p < 0.01$), in studies with a higher % of males ($p < 0.01$), in studies where controls had a higher level of education ($p < 0.01$), and in studies with ascertainment methods other than the CAARMS ($p = 0.001$). *Medium effect size suggests **poorer attention-working memory** in high-risk individuals;* 13 studies, d = -0.39, 95%CI -0.51 to -0.26, $p < 0.05$, I^2 = 57.4%, $p < 0.001$ Moderator analysis revealed smaller effect sizes in more recent publications ($p < 0.02$), in studies with older samples ($p = 0.05$), and in studies with ascertainment methods other than the CAARMS ($p = 0.04$). Larger effect sizes were reported in studies with a higher % of males in the control group only ($p < 0.01$). *Medium effect size suggests **poorer executive functioning** in high-risk individuals;* 6 studies, d = -0.35, 95%CI -0.50 to -0.19, $p < 0.05$, I^2 = 38.2%, $p > 0.10$ Moderator analysis revealed smaller effect sizes in studies where controls had a higher level of education ($p = 0.05$). *Medium effect size suggests **poorer non-verbal memory** in high-risk individuals;* 5 studies, d = -0.35, 95%CI -0.56 to -0.13, $p < 0.05$, I^2 = 40.6%, $p = 0.12$ Moderator analysis revealed smaller effect sizes in samples with higher % of males ($p = 0.05$) and in studies with ascertainment methods other than the CAARMS ($p = 0.45$). *Small effect size suggests **poorer delayed verbal memory and learning** in high-risk individuals;* 3 studies, N = not reported, d = -0.26, 95%CI -0.46 to -0.06, $p < 0.05$, I^2 = 54.8%, $p = 0.05$ No significant moderators. *No significant differences in **motor skills;*** 3 studies, N = not reported, d = -0.16, 95%CI -0.36 to -0.03, $p > 0.05$, I^2 = 0%, $p = 0.47$ No moderator analyses.	
Consistency in results	Consistent for olfactory functioning, executive functioning, immediate verbal memory, non-verbal memory, and motor skills.
Precision in results	Precise
Directness of results	Direct
Comparison 2	**Cognitive functioning in individuals at clinical high-risk of psychosis who converted to psychosis or did not convert to**

	psychosis vs. controls.
Summary of evidence	**Moderate quality evidence (unclear sample sizes, mostly inconsistent, precise, direct) suggests a medium-sized reduction in olfactory functioning, general cognitive ability, language functioning, visual-spatial ability, memory, attention and executive functioning in high-risk individuals who converted to psychosis vs. controls. There was also a small to medium reduction in olfactory functioning, general cognitive ability, language functioning, verbal memory, and attention in high-risk individuals who did not convert to psychosis vs. controls.**
Cognitive functioning	
*Medium effect size suggests **poorer olfactory functioning** in non-converters vs. controls;* 2 studies, *d* = -0.67, 95%CI -1.15 to -0.19, *p* < 0.05, I^2 not reported *Medium effect size suggests **poorer olfactory functioning** in converters vs. controls;* 2 studies, *d* = -0.84, 95%CI -1.31 to -0.37, *p* < 0.05, I^2 not reported *Medium effect size suggests **poorer general cognitive ability/IQ** in non-converters vs. controls;* 3 studies, *d* = -0.70, 95%CI -1.28 to -0.12, *p* < 0.05, I^2 not reported *Medium effect size suggests **poorer general cognitive ability/IQ** in converters vs. controls;* 3 studies, *d* = -0.81, 95%CI -1.12 to -0.49, *p* < 0.05, I^2 not reported *Medium effect size suggests **poorer language functioning** in non-converters vs. controls;* 6 studies, *d* = -0.33, 95%CI -0.46 to -0.19, *p* < 0.05, I^2 not reported *Medium effect size suggests **poorer language functioning** in converters vs. controls;* 6 studies, *d* = -0.67, 95%CI -0.81 to -0.54, *p* < 0.05, I^2 not reported *Medium effect size suggests **poorer immediate verbal memory** in non-converters vs. controls;* 3 studies, *d* = -0.38, 95%CI -0.62 to -0.14, *p* < 0.05, I^2 not reported *Medium effect size suggests **poorer immediate verbal memory** in converters vs. controls;* 3 studies, *d* = -0.72, 95%CI -1.06 to -0.37, *p* < 0.05, I^2 = 50.7%, *p* = 0.048 *Medium effect size suggests **poorer attention-processing speed** in non-converters vs. controls;* 3 studies, *d* = -0.40, 95%CI -0.59 to -0.21, *p* < 0.05, I^2 not reported *Medium effect size suggests **poorer attention-processing speed** in converters vs. controls;* 3 studies, *d* = -0.56, 95%CI -0.79 to -0.32, *p* < 0.05, I^2 = 54.4%, *p* = 0.04 *No differences in **visual-spatial ability** between non-converters vs. controls;* 2 studies, *d* = -0.49, 95%CI -0.98 to 0.02, *p* > 0.05, I^2 not reported	

Medium effect size suggests ***poorer visual-spatial ability*** *in converters vs. controls;* 2 studies, *d* = -0.78, 95%CI -1.45 to -0.11, *p* < 0.05, I^2 not reported *Medium effect size suggests* ***poorer attention-vigilance*** *in non-converters vs. controls;* 4 studies, *d* = -0.42, 95%CI -0.57 to -0.27, *p* < 0.05, I^2 not reported *Medium effect size suggests* ***poorer attention-vigilance*** *in converters vs. controls;* 4 studies, *d* = -0.61, 95%CI -0.80 to -0.42, *p* < 0.05, I^2 = 30.7%, *p* = 0.15 *Medium effect size suggests* ***poorer attention-working memory*** *in non-converters vs. controls;* 4 studies, *d* = -0.44, 95%CI -0.62 to -0.25, *p* < 0.05, I^2 not reported *Medium effect size suggests* ***poorer attention-working memory*** *in converters vs. controls;* 4 studies, *d* = -0.77, 95%CI -1.18 to -0.35, *p* < 0.05, I^2 = 62.1%, *p* = 0.02 *No differences in* ***executive functioning*** *between non-converters and controls;* 2 studies, *d* = -0.34, 95%CI -0.76 to 0.08, *p* > 0.05, I^2 not reported *Medium effect size suggests* ***poorer executive functioning*** *in converters vs. controls;* 2 studies, *d* = -0.47, 95%CI -0.72 to -0.22, *p* < 0.05, I^2 not reported *No differences in* ***non-verbal memory*** *between non-converters vs. controls;* 3 studies, *d* = -0.34, 95%CI -0.79 to 0.12, *p* > 0.05, I^2 not reported *Medium effect size suggests* ***poorer non-verbal memory*** *in converters vs. controls;* 3 studies, *d* = -0.79, 95%CI -1.36 to -0.22, *p* < 0.05, I^2 = 58.9%, *p* = 0.09 *No differences in* ***delayed verbal memory and learning*** *between non-converters vs. controls;* 1 study, *d* = -0.34, 95%CI -0.75 to 0.07, *p* > 0.05 *Small effect size suggests* ***poorer delayed verbal memory and learning*** *in converters vs. controls;* 1 study, *d* = -0.52, 95%CI -0.99 to -0.04, *p* < 0.05 *No differences in* ***motor skills*** *between non-converters vs. controls;* 2 studies, *d* = -0.14, 95%CI -0.45 to 0.18, *p* > 0.05, I^2 not reported *No differences in* ***motor skills*** *between converters vs. controls;* 2 studies, *d* = -0.35, 95%CI -0.89 to 0.21, *p* > 0.05, I^2 not reported	
Consistency in results	Consistent for attention-vigilance and non-verbal memory for converters vs. controls.
Precision in results	Imprecise for non-verbal memory and visual-spatial ability in converters vs. controls.
Directness of results	Direct

Hauser M, Zhang JP, Sheridan EM, Burdick KE, Mogil R, Kane JM, Auther A, Carrion RE, Cornblatt BA, Correll CU

Neuropsychological Test Performance to Enhance Identification of Subjects at Clinical High Risk for Psychosis and to Be Most Promising for Predictive Algorithms for Conversion to Psychosis: A Meta-Analysis

Journal of Clinical Psychiatry 2017; 78: e28-e40

View review abstract online

Comparison 1	**Cognitive functioning in individuals at clinical high-risk of psychosis vs. controls.**
Summary of evidence	**Moderate to high quality evidence (large samples, mostly inconsistent, mostly precise, direct) shows medium-sized effects of poorer processing speed, verbal learning, and social cognition and small effects of reduced visual learning, working memory, attention, reasoning and IQ in people at clinical high-risk for psychosis.**

Cognitive functioning

*Significant, medium-sized effect of **poorer processing speed** in people at clinical high-risk;*

12 studies, N = 1,664, g = -0.43, 95%CI -0.61 to -0.24, $p < 0.0002$, $I^2 = 68\%$

This effect was similar in longitudinal studies (follow-up 10.4 months, g = -0.45). The effect was significant in studies using the Controlled Oral Word Association Test, Trail-Making A and B, and digit symbol, but not the Finger Tapping Test.

*Significant, medium-sized effect of **poorer verbal learning** in people at clinical high-risk;*

11 studies, N = 1,132, g = -0.42, 95%CI -0.64 to -0.20, $p < 0.0002$, $I^2 = 67\%$

This effect was smaller in longitudinal studies (follow-up 10.4 months, g = -0.28). The effect was significant in studies using the California Verbal Learning Test, Logical Memory Test and the Rey Auditory Verbal Learning Test.

*Significant, medium-sized effect of **poorer social cognition** in people at clinical high-risk;*

6 studies, N = 755, g = -0.43, 95%CI -0.68 to -0.18, $p = 0.001$, $I^2 = 63\%$

This effect was significant in studies using the False Belief and Strange Story tasks, but not the Eye test.

*Significant, small effect of **poorer visual learning** in people at clinical high-risk;* 5 studies, N = 520, *g* = -0.27, 95%CI -0.47 to -1.03, *p* = 0.002, I^2 = 6% This effect was significant in studies using the Rey-Osterrieth Complex Figure Test. *Significant, small effect of **poorer working memory** in people at clinical high-risk;* 10 studies, N = 1,512, *g* = -0.24, 95%CI -0.49 to 0.005, *p* = 0.05, I^2 = 80% This effect was larger in longitudinal studies (follow-up 10.4 months, *g* = -0.60). The effect was significant in studies using the Letter Number Sequencing Test, but not digits backward or Subject Ordered Pointing Task. *Significant, small effect of **poorer attention** in people at clinical high-risk;* 14 studies, N = 2,038, *g* = -0.17, 95%CI -0.30 to -0.04, *p* = 0.009, I^2 = 46% This effect was larger in longitudinal studies (follow-up 10.4 months, *g* = -0.34). The effect was significant in studies using the Continuous Performance Test and digits forward, but not STROOP or digit span. *Significant, small effect of **poorer reasoning** in people at clinical high-risk;* 8 studies, N = 969, *g* = -0.24, 95%CI -0.49 to 0.004, *p* = 0.05, I^2 = 70% This effect was significant on the Wisconsin Card Sorting Test preservation errors, but not preservation response. *Significant, small effect of l**ower current IQ** in people at clinical high-risk;* 9 studies, N = 1,059, *g* = -0.21, 95%CI -0.35 to -0.07, *p* = 0.003, I^2 = 13% This effect was larger in longitudinal studies (follow-up 10.4 months, *g* = -0.70). The effect was significant in studies using Vocabulary and Block Design. *Significant, small effect of l**ower premorbid IQ** in people at clinical high-risk;* 7 studies, N = 1,260, *g* = -0.25, 95%CI -0.39 to -0.11, *p* < 0.0001, I^2 = 17% This effect was significant in studies using the Mehrfachwortschatztest-B.	
Consistency in results	Inconsistent apart from IQ and visual learning.
Precision in results	Precise apart from visual learning.
Directness of results	Direct
Comparison 2	**Cognitive functioning in individuals at clinical high-risk for psychosis vs. people with first-episode psychosis.**
Summary of evidence	**Moderate to high quality evidence (medium to large samples, mostly inconsistent, mostly precise, direct) shows medium-sized effects of better attention, verbal learning, and working memory, and small effects of better current IQ and speed of processing in people at clinical high-risk of psychosis. There**

	were no differences in reasoning.
Cognitive functioning	
*Significant, medium-sized effect of **better attention** in people at clinical high-risk;* 7 studies, N = 906, *g* = 0.40, 95%CI 0.14 to 0.66, *p* = 0.003, I^2 = 71% *Significant, medium-sized effect of **better verbal learning** in people at clinical high-risk;* 6 studies, N = 655, *g* = 0.39, 95%CI 0.17 to 0.62, *p* = 0.002, I^2 = 44% *Significant, medium-sized effect of **better working memory** in people at clinical high-risk;* 3 studies, N = 418, *g* = 0.41, 95%CI 0.18 to 0.64, *p* < 0.0001, I^2 = 19% *Significant, small to medium-sized effect of **higher current IQ** in people at clinical high-risk;* 3 studies, N = 418, *g* = 0.31, 95%CI 0.11 to 0.51, *p* = 0.003, I^2 = 0% *Significant, small effect of **better speed of processing** in people at clinical high-risk;* 5 studies, N = 527, *g* = 0.29, 95%CI 0.03 to 0.56, *p* = 0.03, I^2 = 55% This effect was significant in studies using the Controlled Oral Word Association Test and Verbal Fluency Semantic Categories, but not Trail-Making B. *No significant differences in **reasoning**;* 3 studies, N = 441, *g* = -0.08, 95%CI -0.26 to 0.42, *p* = 0.642, I^2 = 66%	
Consistency in results	Inconsistent apart from IQ and working memory.
Precision in results	Precise apart from reasoning.
Directness of results	Direct
Comparison 3	**Cognitive functioning in individuals at clinical high-risk of psychosis that converted or did not convert to psychosis vs. controls.**
Summary of evidence	**Moderate to high quality evidence (medium to large samples, mostly consistent, precise, direct) found large effects of poorer speed of processing and poorer verbal learning in converters. There were medium to large effects of poorer visual learning, working memory and IQ in converters. Medium-sized effects were found for poorer attention and reasoning in converters, and poorer verbal learning and current IQ in non-converters. Small effects were found for poorer attention, reasoning, speed of processing and premorbid IQ in non-converters. There were no differences in visual learning and working memory in non-converters.**

Cognitive functioning
*Significant, small effect of **poorer attention** in non-converters vs. controls;*
8 studies, N = 611, *g* = -0.21, 95%CI -0.37 to -0.05, *p* = 0.01, I^2 = 0%
This effect was significant in studies using the Continuous Performance Test, but not digit span.
*Significant, medium-sized effect of **poorer attention** in converters vs. controls;*
8 studies, N = 483, ***g*** = -0.41, 95%CI -0.71 to -0.12, *p* = 0.006, I^2 = 58%
This effect was significant in studies using the Continuous Performance Test and digit span.
*Significant, small effect of **poorer reasoning** in non-converters vs. controls;*
5 studies, N = 420, *g* = -0.34, 95%CI -0.59 to -0.09, *p* = 0.008, I^2 = 38%
This effect was not significant on the Wisconsin Card Sorting Test preservation errors test.
*Significant, medium-sized effect of **poorer reasoning** in converters vs. controls;*
5 studies, N = 328, ***g*** = -0.50, 95%CI -0.73 to -0.27, *p* < 0.0001, I^2 = 0%
This effect was not significant on the Wisconsin Card Sorting Test preservation errors test.
*Significant, small effect of **poorer speed of processing** in non-converters vs. controls;*
7 studies, N = 528, *g* = -0.34, 95%CI -0.53 to -0.16, *p* < 0.0001, I^2 = 0%
This effect was significant on the Trail-Making Test A and Digit Symbol, but not Trail-Making Test B or the Verbal Fluency Test.
*Significant, large effect of **poorer speed of processing** in converters vs. controls;*
7 studies, N = 429, ***g*** = -0.80, 95%CI -1.02 to -0.58, *p* < 0.0001, I^2 = 0%
This effect was significant on the Trail-Making Test A and B, Digit Symbol and the Verbal Fluency Test.
*Significant, medium-sized effect of **poorer verbal learning** in non-converters vs. controls;*
7 studies, N = 489, *g* = -0.54, 95%CI -0.90 to -0.19, *p* = 0.003, I^2 = 66%
This effect was significant in studies using the California Verbal Learning Test, the Logical Memory Test and the Rey Auditory Verbal Learning Test.
*Significant, large effect of **poorer verbal learning** in converters vs. controls;*
7 studies, N = 400, ***g*** = -0.87, 95%CI -1.22 to -0.52, *p* < 0.0001, I^2 = 58%
This effect was significant in studies using the California Verbal Learning Test, the Rey Auditory Verbal Learning Test, but not the Logical Memory Test.
*No significant differences in **visual learning** in non-converters vs. controls;*
4 studies, N = 285, *g* = -0.16, 95%CI -0.39 to 0.07, *p* = 0.18, I^2 = 0%
*Significant, medium to large effect of **poorer visual learning** in converters vs. controls;*
4 studies, N = 240, *g* = -0.75, 95%CI -1.06 to -0.44, *p* < 0.0001, I^2 = 22%

Cognition in high-risk groups

*No significant differences in **working memory** in non-converters vs. controls;* 6 studies, N = 427, *g* = -0.31, 95%CI -0.65 to 0.03, *p* = 0.07, I^2 = 65% *Significant, medium to large effect of **poorer working memory** in converters vs. controls;* 6 studies, N = 344, *g* = -0.63, 95%CI -0.89 to -0.37, *p* < 0.0001, I^2 = 24% *Significant, medium-sized effect of **lower current IQ** in non-converters vs. controls;* 3 studies, N = 236, *g* = -0.61, 95%CI -0.88 to -0.34, *p* < 0.0001, I^2 = 3% *Significant, medium to large effect of **lower current IQ** in converters vs. controls;* 3 studies, N = 174, *g* = -0.72, 95%CI -1.04 to -0.39, *p* < 0.0001, I^2 = 0% *Significant, small effect of **lower premorbid IQ** in non-converters vs. controls;* 6 studies, N = 424, *g* = -0.30, 95%CI -0.49 to -0.11, *p* = 0.002, I^2 = 0% *Significant, medium to large effect of **lower premorbid IQ** in converters vs. controls;* 6 studies, N = 406, *g* = -0.75, 95%CI -1.01 to -0.49, *p* < 0.0001, I^2 = 8%	
Consistency in results	Consistent apart from working memory in non-converters, verbal learning in non-converters and converters, and attention in converters.
Precision in results	Precise
Directness of results	Direct

Explanation of acronyms

CI = confidence interval, *d* = Cohen's d and *g* = Hedges' *g* = standardised mean differences (see below for interpretation of effect sizes), I^2 = percentage of variance in results across studies, N = number of participants, *p* = statistical probability of obtaining that result (*p* < 0.05 generally regarded as significant), Q_B = Q statistic (chi-square) for the test of heterogeneity in results across groups of studies, Q_w = Q statistic (chi-square) for the test of heterogeneity in results within a group of studies, vs. = versus

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[10].

† 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) that 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. Less than 0.4 represents a small effect, around 0.5 a medium effect, and over 0.8 represents a large effect[10].

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[11]. 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 between variables. They can provide an indirect 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. Unstandardized (*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. Standardized 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;[10]

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

§ 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.[12]

‖ 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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