

## Learning

### Introduction

Learning is the ability to acquire, or change, existing knowledge, behaviours, or skills. There are two distinct forms of learning: explicit (or declarative) learning occurs during a high level of consciousness regarding specific learnt content, for example, memorising information for an exam. Implicit (or procedural) learning is less conscious and refers to learning that is gained from task performance, for example, juggling. Explicit verbal learning can be measured with the Hopkins Verbal Learning test, the California Verbal Learning test and verbal list-learning, for example. The Brief Visuospatial memory test, the Rey design learning test, the Rey complex figure test, and visual reproduction all measure explicit visual learning. Implicit learning can be measured using the Serial Reaction Time task where learning is inferred from reduced reaction time to stimuli.

### Method

We have included only systematic reviews with detailed literature search, methodology, and inclusion/exclusion criteria that were published in full text, in English, from the year 2000. Reviews were identified by searching the databases MEDLINE, EMBASE, and PsycINFO. Reviews with pooled data are prioritized for inclusion. Reviews reporting fewer than 50% of items on the Preferred Reporting Items for Systematic Reviews and Meta-Analyses ([PRISMA](#)<sup>1</sup>) checklist have been excluded from the library. The evidence was graded guided by the Grading of Recommendations Assessment, Development and Evaluation (GRADE) Working Group approach<sup>2</sup>. 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 19 systematic reviews that met our inclusion criteria<sup>3-21</sup>.

- Compared to controls, moderate to high quality evidence suggests a medium to large effect of poorer performance in verbal learning cued and free recall, verbal span, verbal paired associate learning, verbal recognition, and serial reaction time in people with schizophrenia.
- Compared to people with bipolar disorder, moderate to high quality evidence finds medium-sized effects suggesting people with schizophrenia show impaired performance on verbal and visual learning tasks.
- Moderate to high quality evidence finds a medium-sized effect suggesting people with schizoaffective disorder show impaired performance on verbal learning tasks compared to people with bipolar disorder. Moderate to high quality evidence finds small effects suggesting people with schizophrenia show impaired performance on verbal and visuospatial learning tasks compared to people with schizoaffective disorder.
- Moderate to high quality evidence suggests a small to medium-sized association between increased negative or disorganised symptoms and poorer visual and verbal learning.
- Overall, moderate to high quality evidence finds greater improvements in explicit, but not implicit learning in people with schizophrenia taking second-generation antipsychotics than first-generation antipsychotics. Patients receiving second-generation olanzapine, clozapine or risperidone, or first-generation haloperidol, showed improvements, but patients receiving second-generation quetiapine show no improvement.
- Moderate to high quality evidence showed small associations between better verbal

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learning and better community functioning, social behavior, problem-solving and social skills. Moderate to low quality evidence finds better work capacity is associated with better verbal learning.

- Moderate to high quality evidence suggests medium to strong associations between increased verbal and visual learning and increased memory, executive functioning, attention, processing speed, reasoning, abstraction, and flexibility.
- High quality evidence found a small impairment in learning in smokers vs. non-smokers with schizophrenia. Moderate to high quality evidence suggests a small effect of better verbal learning and memory in people with a psychotic disorder and a substance use disorder than people with a psychotic disorder without a substance use disorder.
- In people at clinical high risk for psychosis, moderate to high quality evidence finds medium-sized effects of poorer verbal and visual learning compared to controls. There were large effects in those who converted to psychosis, and small to medium-sized effects in non-converters. When compared to people with first-episode psychosis, people at clinical high-risk showed better verbal and visual learning.

*Bogaty SER, Lee RSC, Hickie IB, Hermens DF*

**Meta-analysis of neurocognition in young psychosis patients with current cannabis use**

**Journal of Psychiatric Research 2018; 99: 22-32**

[View review abstract online](#)

<b>Comparison</b>	<b>Verbal learning in people with psychosis and current cannabis use vs. people with psychosis with no cannabis use.</b>
<b>Summary of evidence</b>	<b>High quality evidence (large sample, consistent, precise, direct) no differences in verbal learning.</b>
<b>Verbal learning</b>	
<i>There were no significant differences in verbal learning; 8 studies, N = 1,153, g = -0.39, 95%CI -0.80 to 0.04, p &lt; 0.10, I<sup>2</sup> = 89%</i>	
<b>Consistency in results<sup>‡</sup></b>	Consistent for IQ only.
<b>Precision in results<sup>§</sup></b>	Precise, apart from working memory, verbal fluency and sustained attention.
<b>Directness of results<sup>  </sup></b>	Direct

*Catalan A, Salazar De Pablo G, Aymerich C, Damiani S, Sordi V, Radua J, Oliver D, McGuire P, Giuliano AJ, Stone WS, Fusar-Poli P*

**Neurocognitive Functioning in Individuals at Clinical High Risk for Psychosis: A Systematic Review and Meta-analysis**

**JAMA Psychiatry 2021; 78(8): 859-67**

[View review abstract online](#)

<b>Comparison 1</b>	<b>Verbal and visual learning in individuals at clinical high-risk of psychosis vs. controls.</b>
<b>Summary of evidence</b>	<b>Moderate to high quality evidence (large samples, inconsistent, precise, direct) shows medium-sized effects of poorer verbal</b>

	<b>and visual learning in people at clinical high-risk of psychosis compared to controls.</b>
<b>Verbal and visual learning</b>	
<p><i>Medium-sized effects showed people at clinical high-risk of psychosis performed more poorly than controls on verbal and visual learning tasks:</i></p> <p>Verbal learning: 21 studies, N = 3,559, <math>g = -0.51</math>, 95%CI -0.63 to -0.39, <math>p &lt; 0.001</math> (Hopkins Verbal Learning Test - Revised, Rey Auditory Verbal Learning Test, and the California Verbal Learning Test)</p> <p>Visual learning: 13 studies, N = 2,533, <math>g = -0.43</math>, 95%CI -0.57 to -0.29, <math>p &lt; 0.001</math> (Brief Visuospatial Memory Test - Revised, and the Wechsler Memory Scale - Immediate Visual Memory. There were no differences on the Rey-Osterrieth Complex Figure - Immediate Recall)</p>	
<b>Consistency in results</b>	Authors report moderate to high heterogeneity
<b>Precision in results</b>	Precise
<b>Directness of results</b>	Direct
<b>Comparison 2</b>	<b>Verbal learning in individuals at high-risk of psychosis who made the transition to psychosis vs. individuals at high-risk of psychosis who did not make the transition to psychosis.</b>
<b>Summary of evidence</b>	<b>Moderate quality evidence (mixed sample sizes, inconsistent, some imprecision, direct) shows a medium-sized effect of poorer verbal learning 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.</b>
<b>Verbal learning</b>	
<p><i>A medium-sized effect showed people at clinical high-risk of psychosis who transitioned to psychosis performed more poorly than people at clinical high-risk of psychosis who did not transition to psychosis on verbal learning tasks:</i></p> <p>3 studies, N = 151, <math>g = -0.58</math>, 95%CI -1.12 to -0.05, <math>p = 0.03</math> (California Verbal Learning Test)</p>	
<b>Consistency in results</b>	Authors report moderate to high heterogeneity
<b>Precision in results</b>	Some imprecision
<b>Directness of results</b>	Direct

<b>Comparison 3</b>	<b>Cognitive functioning in individuals at clinical high-risk for psychosis vs. people with first-episode psychosis</b>
<b>Summary of evidence</b>	<b>Moderate quality evidence (mixed sample size, inconsistent, some imprecision, direct) shows medium-sized effects of better verbal learning, general intelligence, and executive functioning in individuals at high-risk of psychosis compared to people with first-episode psychosis. There were no differences in premorbid intelligence or processing speed.</b>
<b>Cognitive functioning</b>	
<p><i>Medium-sized effects showed people at clinical high-risk of psychosis performed better than people with first-episode psychosis on:</i></p> <p><b>General intelligence:</b> 3 studies, N = 206, <math>g = 0.63</math>, 95%CI 0.35 to 0.91, <math>p &lt; 0.001</math> (Wechsler - Full Scale IQ)</p> <p><b>Verbal learning:</b> 6 studies, N = 625, <math>g = 0.46</math>, 95%CI 0.30 to 0.62, <math>p &lt; 0.001</math> (Hopkins Verbal Learning Test, California Verbal Learning Test)</p> <p><b>Executive functioning:</b> 8 studies, N = 843, <math>g = 0.34</math>, 95%CI 0.11 to 0.56, <math>p &lt; 0.001</math> (Wisconsin Card Sorting Test – Categories, Perseverative errors, STROOP - Interference)</p> <p><i>There were no significant differences on;</i></p> <p><b>Processing speed:</b> 3 studies, N = 321, <math>g = 0.38</math>, 95%CI -0.08 to 0.84, <math>p = 0.10</math> (Trail Making Test - Part A)</p> <p><b>Premorbid intelligence:</b> 3 studies, N = 172, <math>g = -0.14</math>, 95%CI -0.74 to 0.47, <math>p = 0.66</math> (National Adult Reading Test)</p>	
<b>Consistency in results</b>	Authors report moderate to high heterogeneity
<b>Precision in results</b>	Some imprecision
<b>Directness of results</b>	Direct

*Christensen T*

**The influence of neurocognitive dysfunctions on work capacity in schizophrenia patients: a systematic review of the literature**

**International Journal of Psychiatry in Clinical Practice 2007; 11(2): 89-101**



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<b>Comparison</b>	<b>Association between work capacity and verbal learning in people with schizophrenia.</b> <b>Note: work capacity is the ability to obtain and maintain competitive work and work behaviours and skills.</b>
<b>Summary of evidence</b>	<b>Moderate to low quality evidence (medium-sized sample, direct, unable to assess consistency or precision) suggests that lower levels of work capacity are associated with poor verbal learning and language.</b>
<b>Verbal learning</b>	
5 studies (N = 348) reported that poor <i>verbal learning and language</i> was associated with worse work behaviour improvements, work performance, less hours worked, wages earned and contact with employment specialist.	
<b>Consistency in results</b>	Unable to assess; no measure of consistency is reported.
<b>Precision in results</b>	Unable to assess; no measure of precision is reported.
<b>Directness of results</b>	Direct

*Coustals N, Martelli C, Brunet-Lecomte M, Petillion A, Romeo B, Benyamina A*

**Chronic smoking and cognition in patients with schizophrenia: A meta-analysis**

Schizophrenia Research 2020; 222: 113-21

[View review abstract online](#)

<b>Comparison</b>	<b>Learning in smokers vs. non-smokers with schizophrenia.</b>
<b>Summary of evidence</b>	<b>High quality evidence (large samples, consistent, precise, direct) found a small impairment in learning in smokers vs. non-smokers with schizophrenia.</b>
<b>Learning</b>	



*A small effect showed chronic smoking in patients with schizophrenia was associated with significant impairment in learning;*

8 studies, N = 2,840, SMD = -0.18, 95%CI -0.26 to -0.10,  $p < 0.001$ ,  $I^2 = 0\%$

<b>Consistency in results</b>	Consistent
<b>Precision in results</b>	Precise
<b>Directness of results</b>	Direct

*de Gracia Domingues M, Viechtbauer W, Simons C, van Os J*

**Are psychotic psychopathology and neurocognition orthogonal? A systematic review of their associations**

**Psychological Bulletin 2009; 135(1): 157-171**

[View review abstract online](#)

<b>Comparison</b>	<b>Association between learning and symptom dimensions in people with non-affective psychosis.</b>
<b>Summary of evidence</b>	<b>Moderate to high quality evidence (unclear sample size, direct, precise, consistent) suggests small to medium-sized associations between increased negative or disorganised symptoms and poorer visual and verbal learning.</b>

**Memory**

*A significant small to medium association between increased negative symptoms and lower;*  
 Verbal learning and memory: 20 studies,  $\mu_p^\dagger = -0.214$ , 95%CI -0.279 to -0.146,  $p = 0.00$ ,  $I^2 = 54\%$   
 Visual learning and memory: 13 studies,  $\mu_p = -0.126$ , 95%CI -0.202 to -0.047,  $p = 0.001$ ,  $I^2 = 29\%$   
*A significant small to medium association between increased disorganised symptoms and lower;*  
 Visual learning and memory: 6 studies,  $\mu_p = -0.206$ , 95%CI -0.331 to -0.074,  $p = 0.002$ ,  $I^2 = 42\%$   
 Verbal learning and memory: 13 studies,  $\mu_p = -0.169$ , 95%CI -0.27 to -0.064,  $p = 0.001$ ,  $I^2 = 59\%$   
*No association with positive symptoms;*  
 Verbal learning and memory: 17 studies,  $\mu_p = -0.021$ , 95%CI -0.096 to 0.054,  $p = 0.578$ ,  $I^2 = 47\%$   
 Visual learning and memory: 9 studies,  $\mu_p = -0.005$ , 95%CI -0.089 to 0.079,  $p = 0.91$ ,  $I^2 = 0\%$



**Learning**

<b>Consistency</b>	Consistent
<b>Precision</b>	Precise
<b>Directness</b>	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](#)

<b>Comparison</b>	<b>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.</b>
<b>Summary of evidence</b>	<b>Moderate to high quality evidence (unclear sample size, consistent, precise, direct) suggests small to medium-sized effects of poor visual learning 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.</b>
<b>Verbal and visual learning</b>	
<p><i>Significant, medium effect of poor visual learning in people at clinical high risk for psychosis who transitioned to psychosis compared with those who did not transition to psychosis;</i></p> <p style="text-align: center;">5 studies, <math>g = -0.40</math>, 95%CI -0.68 to -0.13, <math>p = 0.004</math>, Q-test <math>p = 0.733</math></p> <p style="text-align: center;"><i>No significant differences between groups in verbal learning;</i></p> <p style="text-align: center;">8 studies, <math>g = -0.79</math>, 95%CI -1.82 to 0.25, <math>p = 0.137</math>, Q-test <math>p &lt; 0.0001</math></p>	
<b>Consistency</b>	Consistent for visual learning only
<b>Precision</b>	Precise for visual learning only
<b>Directness</b>	Direct



*Dickinson D, Gold JM*

**Less unique variance than meets the eye: Overlap among traditional neuropsychological dimensions in schizophrenia**

Schizophrenia Bulletin 2008; 34(3): 423-434

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<b>Comparison</b>	<b>Association between individual and composite measures of learning and other neuropsychological tests in people with schizophrenia.</b>
<b>Summary of evidence</b>	<b>Moderate to high quality evidence (large sample, direct, unable to assess consistency, precise) showed medium to strong associations between increased scores on verbal and visual learning and increased scores on other Measurement and Treatment Research to Improve Cognition in Schizophrenia (MATRICS) domains including memory, executive functioning, attention, processing speed, reasoning, abstraction and flexibility.</b>
<b>Verbal and visual learning</b>	
<p style="text-align: center;">9 studies (N = 1,860)</p> <p>Meta-analysis combined multiple correlations within each study into a single study-level effect size, and then calculated an overall weighted effect size between studies.</p> <p>Weighted effect size of these 9 studies indicated a significant correlation across composite MATRICS cognitive scores; such that increased performance on reasoning tasks was associated with increased performance on other cognitive tests, <math>r = 0.45</math>, 95%CI 0.35 to 0.54, <math>p &lt; 0.001</math>.</p> <p>1 study (N = 40) reported a medium association between increased verbal learning (logical memory, paired associates, CVLT variables) and visual learning (visual reproduction variables) and increased working memory and processing speed; <math>r = 0.35</math>, 95%CI 0.21 to 0.47.</p> <p>1 study (N = 148) reported a strong association between increased verbal learning (CVLT and logical memory variables) and visual learning (visual reproduction variables) and increased processing speed and executive functioning; <math>r = 0.61</math>, 95%CI 0.56 to 0.66.</p> <p>1 study (N = 219) reported a medium association between increased verbal learning (CVLT variables) and increased working memory and executive functioning; <math>r = 0.34</math>, 95%CI 0.27 to 0.40.</p> <p>1 study (N = 53) reported a strong association between increased verbal learning (logical memory, CVLT and Penn word memory test) and increased executive functioning; <math>r = 0.54</math>, 95%CI 0.40 to 0.66.</p>	

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1 study (N = 45) reported a strong association between increased verbal learning (CVLT) and visual learning (visual reproduction variables) and increased executive functioning and attention;  $r = 0.52$ , 95%CI 0.38 to 0.64.

1 study (N = 1,123) reported a strong association between increased verbal learning (HVL variables) and increased processing speed, reasoning, working memory, vigilance;  $r = 0.50$ ; 95%CI 0.47 to 0.53.

1 study (N = 113) reported a strong association between increased verbal learning (Spanish verbal learning test, verbal fluency variables, Trails B) and increased attention and abstraction and flexibility;  $r = 0.45$ , 95%CI 0.35 to 0.54.

1 study (N = 118) reported a medium association between increased scores on individual measures of learning (CVLT) and increased scores on Rey complex figure memory, category fluency, Stroop (colour and word) and Gordon's CPT;  $r = 0.30$ , 95%CI 0.24 to 0.36.

1 study (N = 1,123 to 1,332) reported a strong association between increased scores on individual measures of learning (HVL) and increased scores on category and letter fluency, digit symbol, WCST, WISC mazes, visuospatial working memory, letter-number sequencing and identical pairs CPT variables;  $r = 0.40$ , 95%CI 0.37 to 0.44.

1 study (N = 140) reported a medium association between increased scores on individual measures of learning (verbal list learning) and increased scores on digit sequencing, category and letter fluency, symbol digit coding and Tower of London;  $r = 0.33$ , 95%CI 0.24 to 0.41.

1 study (N = 32) reported a strong association between increased scores on individual measures of learning (HVL) and increased scores on WCST (perseverative errors), Penn conditional exclusion test with letter fluency, trails A and B and digit symbol;  $r = 0.40$ , 95%CI 0.28 to 0.50.

1 study (N = 30) reported a medium association between increased scores on individual measures of learning (Rey AVLT) and increased scores on symbol digit, WCST, identical pairs CPT, letter number sequencing, trials A and B;  $r = 0.30$ , 95%CI 0.18 to 0.41.

1 study (N = 27) reported a medium association between increased scores on individual measures of learning (visual object learning test) and increased scores on working memory tasks, digit span, Dot working memory test with Penn CPT, Benton visual retention test, Penn face memory, Penn abstraction, inhibition and working memory test;  $r = 0.46$ , 95%CI 0.29 to 0.61.

<b>Consistency</b>	Unable to assess; no measure of consistency is reported.
<b>Precision</b>	Precise
<b>Directness</b>	Direct

*Donoghue K, Doody GA*

**Effect of Illegal Substance Use on Cognitive Function in Individuals With a**

**Psychotic Disorder, A Review and Meta-Analysis**

Neuropsychology 2012; 26 (6): 785-801

[View review abstract online](#)

<b>Comparison</b>	<b>Cognitive functioning in people with a psychotic disorder and a substance use disorder vs. people with a psychotic disorder without a substance use disorder.</b>
<b>Summary of evidence</b>	<b>Moderate to high quality evidence (medium to large samples, consistent, precise, direct) suggests a small effect of better verbal learning and memory in people with a psychotic disorder and a substance use disorder than people with a psychotic disorder without a substance use disorder.</b>
<b>Cognitive functioning in people with a polysubstance use disorder</b>	
<i>A significant small effect suggests people with a psychotic disorder and a polysubstance use disorder showed better verbal learning and memory than people with a psychotic disorder without a substance use disorder;</i>	
5 studies, N = 296, $g = 0.257$ , 95%CI 0.011 to 0.503, $p = 0.040$ , $I^2 = 0\%$ , $p = 0.780$	
<b>Cognitive functioning in people with a cannabis use disorder</b>	
<i>A significant small effect suggests people with a psychotic disorder and a cannabis use disorder showed better verbal learning and memory than people with a psychotic disorder without a substance use disorder;</i>	
3 studies, N = 551, $g = 0.351$ , 95%CI 0.179 to 0.523, $p < 0.001$ , $I^2 = 0\%$ , $p = 0.910$	
<b>Consistency in results</b>	Consistent
<b>Precision in results</b>	Precise
<b>Directness of results</b>	Direct

*Fett AK, Viechtbauer W, Dominguez M, Penn D, van Os J, Krabbendam L*

**The relationship between neurocognition and social cognition with functional outcomes in schizophrenia: A meta-analysis**

Neuroscience and Biobehavioural Reviews 2011; 35: 573-588

[View review abstract online](#)

<b>Comparison</b>	<b>Association between functional outcomes (community function, social behaviour, social problem solving, social skills) and performance on various cognitive domains in patients with schizophrenia.</b>
<b>Summary of evidence</b>	<b>Moderate to high quality evidence (mixed sample, direct, mostly consistent, precise) showed small associations between better community functioning, social behavior, problem-solving ability and social skills and better verbal and visual learning.</b>
<b>Community functioning (work performance, social interaction)</b>	
<p><i>Significant, small association between increased performance on verbal learning tasks and greater community functioning;</i></p> <p>17 studies, N = 1,125, <math>r = 0.26</math>, 95%CI 0.15 to 0.37, <math>p &lt; 0.001</math>, <math>Q_w = 69.54</math>, <math>I^2 = 71.65\%</math>, <math>p &lt; 0.05</math></p> <p><i>Significant weak association between increased performance on visual learning task and greater community functioning;</i></p> <p>6 studies, N = 230, <math>r = 0.20</math>, 95%CI 0.07 to 0.33, <math>p = 0.003</math>, <math>Q_w = 2.90</math>, <math>I^2 = 0\%</math>, <math>p &gt; 0.05</math></p>	
<b>Social behaviour</b>	
<p><i>Significant, small association between increased performance on verbal learning tasks and improved social behavior:</i></p> <p>4 studies, N = 253, <math>r = 0.32</math>, 95%CI 0.15 to 0.47, <math>p &lt; 0.001</math>, <math>Q_w = 4.84</math>, <math>I^2 = 39.22\%</math>, <math>p &gt; 0.05</math></p> <p><i>Significant small association between better performance on visual learning task and improved social behavior;</i></p> <p>4 studies, N = 122, <math>r = 0.30</math>, 95%CI 0.10 to 0.47, <math>p = 0.002</math>, <math>Q_w = 3.47</math>, <math>I^2 = 11.76\%</math>, <math>p &gt; 0.05</math></p>	
<b>Social problem solving</b>	
<p><i>Significant small association between increased performance on verbal learning tasks and greater social problem solving;</i></p> <p>4 studies, N = 117, <math>r = 0.26</math>, 95%CI 0.07 to 0.43, <math>p = 0.003</math>, <math>Q_w = 0.44</math>, <math>I^2 = 0\%</math>, <math>p &gt; 0.05</math></p>	
<b>Social skills</b>	



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*Significant small association between increased performance on verbal learning task and better social skills;*

7 studies, N = 250,  $r = 0.18$ , 95%CI 0.06 to 0.31,  $p = 0.005$ ,  $Q_w = 8.54$ ,  $I^2 = 0\%$ ,  $p > 0.05$

*Significant small association between increased performance on visual learning task and better social skills;*

4 studies, N = 149,  $r = 0.28$ , 95%CI 0.07 to 0.46,  $p = 0.008$ ,  $Q_w = 5.22$ ,  $I^2 = 30.81\%$ ,  $p > 0.05$

<b>Consistency</b>	Consistent, apart from community functioning.
<b>Precision</b>	Precise
<b>Directness</b>	Direct

*Forbes NF, Carrick LA, McIntosh AM, Lawrie SM*

**Working memory in schizophrenia: a meta-analysis**

Psychological Medicine 2009; 39: 889-905

[View review abstract online](#)

<b>Comparison</b>	Verbal learning in people with schizophrenia vs. controls.
<b>Summary of evidence</b>	<b>Moderate to high quality evidence (unclear sample size, direct, consistent, precise) suggests medium to large effects of poorer verbal learning List A trial 1, verbal learning List B and verbal span tasks without manipulation in people with schizophrenia. Moderate quality evidence (inconsistent) finds medium to large effects of poorer verbal paired associate learning, verbal learning test list A trail 5, list A trial 6 (cued and free recall), total list A 1-5, verbal recall test, verbal span tasks with manipulation, and verbal recognition test.</b>

**Verbal learning**

*A significant large effect size suggests poorer performance on the following learning tests in people with schizophrenia compared with controls;*

Verbal paired associate learning test: 18 studies,  $d = -0.88$ , 95%CI -1.07 to -0.69,  $p < 0.001$ ,  $I^2 = 64.0$ ,  $p < 0.001$

Verbal learning test: List A Trial 1: 11 studies,  $d = -1.01$ , 95%CI -1.26 to -0.76,  $p < 0.001$ ,  $I^2 = 62.1$ ,  $p = 0.36$

Verbal learning test: List A Trial 5: 13 studies,  $d = -1.25$ , 95%CI -1.54 to -0.97,  $p < 0.001$ ,  $I^2 = 78.8$ ,  $p < 0.001$

Verbal learning test: List A Trial 6, cued: 6 studies,  $d = -0.98$ , 95%CI -1.32 to -0.65,  $p < 0.001$ ,  $I^2 = 59.2$ ,  $p = 0.031$

Verbal learning test: List A Trial 6, free recall: 13 studies,  $d = -1.08$ , 95%CI -1.35 to -0.80,  $p < 0.001$ ,  $I^2 = 76.6$ ,  $p < 0.001$

Verbal learning test: Total list A, Trials 1-5: 28 studies,  $d = -1.32$ , 95%CI -1.48 to -1.17,  $p < 0.001$ ,  $I^2 = 60.4$ ,  $p < 0.001$

Verbal learning test: List B: 6 studies,  $d = -0.92$ , 95%CI -1.19 to -0.65,  $p < 0.001$ ,  $I^2 = 40.4$ ,  $p = 0.136$

Verbal recall test: 24 studies,  $d = -1.21$ , 95%CI -1.39 to -1.03,  $p < 0.001$ ,  $I^2 = 53.3$ ,  $p = 0.001$

Verbal span tasks involving manipulation: 9 studies,  $d = -1.02$ , 95%CI -1.32 to -0.71,  $p < 0.001$ ,  $I^2 = 67.6$ ,  $p = 0.002$

*A significant medium effect size suggests poorer performance on the following verbal learning tests in people with schizophrenia compared with controls;*

Verbal span tasks without manipulation: 7 studies,  $d = -0.72$ , 95%CI -0.91 to -0.51,  $p < 0.001$ ,  $I^2 = 0$ ,  $p = 0.433$

Verbal recognition test: 19 studies,  $d = -0.63$ , 95%CI -0.84 to -0.42,  $p < 0.001$ ,  $I^2 = 58.9$ ,  $p = 0.001$

Meta-regression analysis suggests a significant association between longer duration of illness and poorer performance on verbal learning test cued recall post-distraction ( $b = -0.037$ ,  $p = 0.001$ ) and verbal learning test free recall post-distraction ( $b = -0.0339$ ,  $p = 0.015$ ).

Dose of chlorpromazine was associated with performance on verbal list learning list 1 ( $b = -0.0026$ ,  $p < 0.001$ ), verbal list learning list 5 ( $b = -0.0027$ ,  $p < 0.001$ ), total recall on verbal learning tests recall trials ( $b = -0.0013$ ,  $p < 0.001$ ) and verbal learning test, short delay, free recall ( $b = -0.002$ ,  $p = 0.01$ ).

Verbal list learning list 1 was associated with increased positive symptoms ( $b = 0.09$ ,  $p = 0.35$ ) and negative symptoms ( $b = 0.13$ ,  $p = 0.019$ ).

<b>Consistency</b>	Inconsistent for all except verbal learning list A trial 1, List B and verbal span task without manipulation.
<b>Precision</b>	Precise
<b>Directness</b>	Direct

*Guilera G, Pino O, Gomez-Benito J, Rojo JE*

**Antipsychotic effects on cognition in schizophrenia: A meta-analysis of**



**randomised control trials**

The European Journal of Psychiatry 2009; 23(2): 77-89

[View review abstract online](#)

<b>Comparison</b>	<b>Implicit learning in people with schizophrenia on second generation antipsychotics vs. first generation antipsychotics.</b>
<b>Summary of evidence</b>	<b>Moderate to low quality evidence (small sample, direct, precise, unable to assess consistency) finds no difference in automatic or procedural learning in people with schizophrenia receiving second-generation antipsychotics compared with those receiving first-generation antipsychotics.</b>
<b>Implicit learning</b>	
<i>No significant difference in people with schizophrenia receiving second generation antipsychotics compared with first generation antipsychotics;</i> 2 RCTs, N = 85, g = 0.27, 95%CI -0.13 to 0.64, p = 0.23	
<b>Consistency</b>	Unable to assess; no measure of consistency is reported.
<b>Precision</b>	Precise
<b>Directness</b>	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](#)

<b>Comparison 1</b>	<b>Learning in individuals at clinical high-risk of psychosis vs. controls.</b>
<b>Summary of evidence</b>	<b>Moderate to high quality evidence (medium to large samples,</b>

	<b>inconsistent or imprecise, direct) shows medium-sized effects of poorer verbal and visual learning in people at clinical high-risk for psychosis.</b>
<b>Verbal and visual learning</b>	
<p><i>Significant, medium-sized effect of poorer verbal learning in people at clinical high-risk;</i> 11 studies, N = 1,132, <math>g = -0.42</math>, 95%CI -0.64 to -0.20, <math>p &lt; 0.0002</math>, <math>I^2 = 67\%</math></p> <p>This effect was smaller in longitudinal studies (follow-up 10.4 months, <math>g = -0.28</math>). The effect was significant in studies using the California Verbal Learning Test, Logical Memory Test and the Rey Auditory Verbal Learning Test.</p> <p><i>Significant, small effect of poorer visual learning in people at clinical high-risk;</i> 5 studies, N = 520, <math>g = -0.27</math>, 95%CI -0.47 to -1.03, <math>p = 0.002</math>, <math>I^2 = 6\%</math></p> <p>This effect was significant in studies using the Rey-Osterrieth Complex Figure Test.</p>	
<b>Consistency in results</b>	Inconsistent for verbal learning, consistent for visual learning.
<b>Precision in results</b>	Precise for verbal learning, imprecise for visual learning.
<b>Directness of results</b>	Direct
<b>Comparison 2</b>	<b>Learning in individuals at clinical high-risk for psychosis vs. people with first-episode psychosis.</b>
<b>Summary of evidence</b>	<b>Moderate to high quality evidence (large sample, inconsistent, precise, direct) shows a medium-sized effect of better verbal learning in people at clinical high-risk of psychosis compared to people with first-episode psychosis.</b>
<b>Verbal learning</b>	
<p><i>Significant, medium-sized effect of better verbal learning in people at clinical high-risk;</i> 6 studies, N = 655, <math>g = 0.39</math>, 95%CI 0.17 to 0.62, <math>p = 0.002</math>, <math>I^2 = 44\%</math></p>	
<b>Consistency in results</b>	Inconsistent
<b>Precision in results</b>	Precise
<b>Directness of results</b>	Direct
<b>Comparison 3</b>	<b>Learning in individuals at clinical high-risk of psychosis that converted or did not convert to psychosis vs. controls.</b>
<b>Summary of evidence</b>	<b>Moderate to high quality evidence (medium to large samples,</b>

	some inconsistency, precise, direct) found large effects of poorer verbal and visual learning in converters. In non-converters, there was a medium-sized effect of poorer verbal learning and no differences in visual learning compared to controls.
<b>Verbal and visual learning</b>	
<p><i>Significant, medium-sized effect of poorer verbal learning in non-converters vs. controls;</i> 7 studies, N = 489, <math>g = -0.54</math>, 95%CI -0.90 to -0.19, <math>p = 0.003</math>, <math>I^2 = 66\%</math> This effect was significant in studies using the California Verbal Learning Test, the Logical Memory Test and the Rey Auditory Verbal Learning Test.</p> <p><i>Significant, large effect of poorer verbal learning in converters vs. controls;</i> 7 studies, N = 400, <math>g = -0.87</math>, 95%CI -1.22 to -0.52, <math>p &lt; 0.0001</math>, <math>I^2 = 58\%</math> This effect was significant in studies using the California Verbal Learning Test, the Rey Auditory Verbal Learning Test, but not the Logical Memory Test.</p> <p><i>No significant differences in visual learning in non-converters vs. controls;</i> 4 studies, N = 285, <math>g = -0.16</math>, 95%CI -0.39 to 0.07, <math>p = 0.18</math>, <math>I^2 = 0\%</math></p> <p><i>Significant, medium to large effect of poorer visual learning in converters vs. controls;</i> 4 studies, N = 240, <math>g = -0.75</math>, 95%CI -1.06 to -0.44, <math>p &lt; 0.0001</math>, <math>I^2 = 22\%</math></p>	
<b>Consistency in results</b>	Consistent for visual learning, inconsistent for verbal learning.
<b>Precision in results</b>	Precise
<b>Directness of results</b>	Direct

<p><i>Li W, Zhou FC, Zhang L, Ng CH, Ungvari GS, Li J, Xiang YT</i> <b>Comparison of cognitive dysfunction between schizophrenia and bipolar disorder patients: A meta-analysis of comparative studies</b>  Journal of Affective Disorders 2020; 274: 652-61 <a href="#">View review abstract online</a></p>	
<b>Comparison</b>	Learning in people with schizophrenia vs. people with bipolar disorder.
<b>Summary of evidence</b>	Moderate to high quality evidence (large sample, inconsistent,

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	<b>precise, direct) finds medium-sized effects suggesting people with schizophrenia show impaired performance on verbal and visual learning tasks compared to people with bipolar disorder.</b>
<b>Learning</b>	
<i>Significant, medium-sized effects suggest people with schizophrenia showed impaired performance on verbal and visual learning tasks compared to people with bipolar disorder;</i>	
Verbal: 12 studies, N = 9,518, SMD = -0.78, 95%CI -0.95 to -0.61, $p < 0.00001$ , $I^2 = 64%$ , $p < 0.001$	
Visual: 11 studies, N = 1,449, SMD = -0.65, 95%CI -0.83 to -0.48, $p < 0.0001$ , $I^2 = 47%$ , $p = 0.04$	
<b>Consistency</b>	Inconsistent
<b>Precision</b>	Precise
<b>Directness</b>	Direct

<i>Lynham AJ, Cleaver SL, Jones IR, Walters JTR</i>	
<b>A meta-analysis comparing cognitive function across the mood/psychosis diagnostic spectrum</b>	
<b>Psychological Medicine 2020; 52(2): 323-331</b>	
<a href="#">View review abstract online</a>	
<b>Comparison 1</b>	<b>Learning in people with schizoaffective disorder vs. bipolar disorder.</b>
<b>Summary of evidence</b>	<b>Moderate to high quality evidence (large sample, inconsistent, precise, direct) finds a medium-sized effect suggesting people with schizoaffective disorder show impaired performance on verbal learning tasks compared to people with bipolar disorder.</b>
<b>Verbal learning</b>	
<i>A significant, medium-sized effect suggests people with schizoaffective disorder showed impaired performance on verbal learning tasks compared to people with bipolar disorder;</i>	
8 studies, N = 1,515, $g = -0.42$ , 95%CI -0.60 to -0.24, $p < 0.00001$ , $Qp = 0.03$	
<b>Consistency</b>	Inconsistent
<b>Precision</b>	Precise

<b>Directness</b>	Direct
<b>Comparison 2</b>	<b>Learning in people with schizophrenia vs. schizoaffective disorder.</b>
<b>Summary of evidence</b>	<b>Moderate to high quality evidence (large samples, some inconsistency, precise, direct) finds small effects suggesting people with schizophrenia show impaired performance on verbal and visuospatial learning tasks compared to people with schizoaffective disorder.</b>
<b>Verbal and visuospatial learning</b>	
<p><i>Significant, small effects suggest people with schizophrenia showed impaired performance on verbal and visuospatial learning tasks compared to people with schizoaffective disorder;</i></p> <p>Verbal: 15 studies, N = 3,414, <math>g = 0.24</math>, 95%CI 0.12 to 0.37, <math>p &lt; 0.00001</math>, <math>Qp = 0.009</math></p> <p>Visuospatial: 6 studies, N = 1,267, <math>g = 0.20</math>, 95%CI 0.02 to 0.38, <math>p = 0.03</math>, <math>Qp = 0.22</math></p>	
<b>Consistency</b>	Inconsistent for verbal learning
<b>Precision</b>	Precise
<b>Directness</b>	Direct

Siebert RJ, Weatherall M, Bell EM

**Is implicit sequence learning impaired in schizophrenia? A meta-analysis**

Brain and Cognition 2008; 67: 351-359

[View review abstract online](#)

<b>Comparison</b>	<b>Implicit learning in people with schizophrenia vs. controls.</b>
<b>Summary of evidence</b>	<b>Moderate to high quality evidence (medium-sized sample, consistent, precise, direct) finds poorer Serial Reaction Time in people with schizophrenia.</b>
<b>Implicit learning</b>	
<p><i>Significant, medium-sized effect of poorer Serial Reaction Time performance in people with schizophrenia;</i></p>	

<p>9 studies, N = 364, <math>d = 0.51</math>, 95%CI 0.30 to 0.73, <math>p &gt; 0.05</math>, <math>I^2 = 0</math>, 95%, <math>p &gt; 0.05</math></p> <p>The authors report a greater change in reaction time from sequences and random blocks for controls than for people with schizophrenia.</p>	
<b>Consistency</b>	Consistent
<b>Precision</b>	Precise
<b>Directness</b>	Direct

<p><i>Stefanopoulou E, Manoharan A, Landau S, Geddes J, Goodwin G, Frangou S</i></p> <p><b>Cognitive functioning in patients with affective disorders and schizophrenia: A meta-analysis</b></p> <p>International Review of Psychiatry 2009; 21(4):336-356</p> <p><a href="#">View review abstract online</a></p>	
<b>Comparison</b>	Verbal learning in people with schizophrenia vs. bipolar disorder.
<b>Summary of evidence</b>	<b>Moderate to high quality (unclear sample size, direct, consistent, precise) evidence shows a small effect of lower performance on the California Verbal Learning Test total free recall subscale, but not on the long delayed free recall or recognition hits subscales in patients with schizophrenia vs. bipolar disorder.</b>
<b>Verbal learning</b>	
<p><i>A significant, small effect of poorer verbal learning on the California Test total free recall subscale in people with schizophrenia, with no differences on the long delayed free recall and recognition hits subscales;</i></p> <p>Total free recall: (number of studies not reported), SMD = 0.39, 95%CI 0.06 to 0.72, <math>p = 0.02</math>, <math>I^2 =</math> not reported, <math>p = 0.71</math></p> <p>Long delayed free recall: SMD = 0.16, 95%CI -0.16 to 0.48, <math>p = 0.33</math>, <math>I^2 =</math> not reported, <math>p = 0.73</math></p> <p>Recognition hits: SMD = 0.07, 95%CI -0.31 to 0.47, <math>p = 0.69</math>, <math>I^2 =</math> not reported, <math>p = 0.50</math></p>	
<b>Consistency</b>	Consistent
<b>Precision</b>	Precise



<b>Directness</b>	Direct
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Ventura J, Helleman GS, Thames AD, Koellner V, Nuechterlein KH

**Symptoms as mediators of the relationship between neurocognition and functional outcome in schizophrenia: a meta-analysis**

Schizophrenia Research 2009; 113(2-3): 189-99

[View review abstract online](#)

<b>Comparison</b>	<b>Association between learning, positive symptoms and negative symptoms in people with schizophrenia.</b>
<b>Summary of evidence</b>	<b>Moderate quality evidence (mixed samples, direct, inconsistent, unable to assess precision) suggests increased negative symptoms but not positive symptoms are significantly associated with poorer working memory, verbal learning and memory, and visual learning and memory. Symptom severity may act as a mediator between memory and functional impairment.</b>
<b>Positive Symptoms</b>	
<i>No significant association was reported;</i> Verbal learning and memory: 10 studies, N = 531, $r = 0.00$ , $p = 0.93$ Visual learning and memory: 4 studies, N = 197, $r = -0.10$ , $p = 0.20$	
<b>Negative Symptoms</b>	
<i>Significant, small association between increased negative symptom severity and poorer;</i> Verbal learning and memory: 23 studies, N = 2,978, $r = -0.21$ , $p < 0.01$ Visual learning and memory: 8 studies, N = 454, $r = -0.16$ , $p < 0.01$ <i>Subgroup analysis examined the potential for negative symptom severity to mediate the effect of neurocognitive performance on functional outcomes;</i> The relationship between verbal learning and memory, and visual learning and memory with community function appears to be at least partially mediated by negative symptom severity, $p < 0.01$ . The relationship between verbal learning and memory, and visual learning and memory with skills	

assessment also appears to be mediated by negative symptom severity,  $p < 0.01$ .

<b>Consistency</b>	Authors report all results are inconsistent.
<b>Precision</b>	Unable to assess; no measure of precision is reported.
<b>Directness</b>	Direct for symptom relationships, indirect subgroup analysis.

*Woodward ND, Purdon SE, Meltzer HY, Zald DH*

**A meta-analysis of neuropsychological change to clozapine, olanzapine, quetiapine, and risperidone in schizophrenia**

**International Journal of Neuropsychopharmacology 2005; 8: 457-472**

[View review abstract online](#)

<b>Comparison</b>	<b>Learning in people with schizophrenia receiving second-generation antipsychotics (clozapine, olanzapine, risperidone and quetiapine) vs. first-generation antipsychotics (various) or pre- to post-treatment comparison with second generation antipsychotics.</b>
<b>Summary of evidence</b>	<b>Moderate to high quality evidence (mixed samples consistent, precise, direct) shows greater improvements in explicit learning in patients receiving second-generation antipsychotics compared with first-generation antipsychotics.</b>  <b>Moderate quality evidence (unable to assess precision) suggests patients receiving olanzapine, clozapine or risperidone show improvement pre- to post-treatment, however patients receiving quetiapine show no improvement in learning.</b>

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*Greater improvements in explicit learning were reported for patients receiving second generation antipsychotics compared with patients receiving first generation antipsychotics;*

14 studies, N= 442,  $g = 0.24$ , 95%CI 0.10 to 0.38,  $p < 0.001$ , Q-test  $p > 0.05$

*Post-treatment, patients receiving olanzapine, clozapine or risperidone showed improved learning;*

Olanzapine: 10 studies, N = 625,  $g = 0.61$ , CI not reported,  $p < 0.006$ , Q-test  $p < 0.05$

Risperidone: 7 studies, N = 251,  $g = 0.41$ , CI not reported,  $p < 0.006$ , Q-test  $p > 0.05$

<p>Clozapine: 10 studies, N = 210, <math>g = 0.31</math>, CI not reported, <math>p &lt; 0.006</math>, Q-test <math>p &gt; 0.05</math>  <i>Patients receiving quetiapine showed no significant improvement post medication;</i>                  Quetiapine: 6 studies, N = 108, <math>g = 0.24</math>, CI not reported, <math>p &gt; 0.05</math>, Q-test <math>p &gt; 0.05</math></p>	
<b>Consistency</b>	Consistent apart from olanzapine.
<b>Precision</b>	Precise for first vs. second generation antipsychotics, unable to assess pre-post comparison.
<b>Directness</b>	Direct

<p><i>Woodward ND, Purdon SE, Meltzer HY, Zald DH</i></p> <p><b>A meta-analysis of cognitive changes with haloperidol in clinical trials of atypical antipsychotics: Dose effects and comparison to practice effects</b></p> <p>Schizophrenia Research 2007; 89: 211-224  <a href="#">View review abstract online</a></p>	
<b>Comparison</b>	Verbal learning in people with schizophrenia receiving haloperidol to assess pre-post treatment effects.
<b>Summary of evidence</b>	Moderate to high quality evidence (mixed samples, consistent, precise, direct) shows improvements on verbal learning after treatment with haloperidol.
<b>Verbal learning</b>	
<p><i>Significant, small effect of improved verbal learning post-treatment;</i>                  All studies: 11 studies, N = 538, <math>g = 0.32</math>, 95%CI 0.19 to 0.43, <math>p &lt; 0.05</math>                  Low dose: 6 studies, N = 371, <math>g = 0.37</math>, 95%CI 0.23 to 0.51, <math>p &lt; 0.05</math>                  High dose: 5 studies, N = 167, <math>g = 0.20</math>, 95%CI 0.00 to 0.40, <math>p &lt; 0.05</math></p>	
<b>Consistency</b>	Authors report all results are consistent (using fixed effects model).
<b>Precision</b>	Precise
<b>Directness</b>	Direct

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### Explanation of acronyms

AVLT = Auditory Verbal Learning Test, CI = Confidence Interval, CPT = Continuous Performance Test, CVLT = California Verbal Learning Test,  $d$  = Cohen's  $d$  and  $g$  = Hedges'  $g$  = standardised mean differences (see below for interpretation of effect size), ES = effect size, HVLT = Hopkins Verbal Learning Test,  $I^2$  = the percentage of the variability in effect estimates that is due to heterogeneity rather than sampling error (chance), MATRICS = Measurement and Treatment Research to Improve Cognition in Schizophrenia, N = number of participants,  $p$  = statistical probability of obtaining that result ( $p < 0.05$  generally regarded as significant), Q = Q statistic for the test of heterogeneity,  $Q_B$  = test for between group differences (heterogeneity between groups of studies for an outcome of interest),  $Q_w$  = test for within group differences (heterogeneity in study results within a group of studies – measure of study consistency),  $r$  = correlation coefficient, RCT = randomised control trial, SMD = standard mean difference, SRT = Serial Reaction Time, vs. = versus, WCST = Wisconsin Card Sorting Task, WISC = Wechsler Intelligence Scale for Children

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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<sup>22</sup>.

† 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<sup>22</sup>.

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  $< 0.2$ <sup>23</sup>. InOR stands for logarithmic OR where a InOR of 0 shows no difference between groups. Hazard ratios measure the effect of an explanatory variable on the hazard or risk of an event.

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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 unforeseen 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

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

calculated from  $Q$  (chi-square) for the test of heterogeneity with the following formula<sup>22</sup>;

§ 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<sup>24</sup>.

|| 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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