# TECHNICAL COMMENTARY

## Autism spectrum disorders

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### Introduction

Autism spectrum disorders are neurodevelopmental conditions characterised by problems in social interaction and communication, and restricted, repetitive behaviours. Symptoms usually appear before three years of age, but can appear later. Autism spectrum disorders are often associated intellectual disability however average-IQ is frequent.

### Method

We have included only systematic reviews (systematic literature search, detailed methodology with inclusion/exclusion criteria) published in full text, in English, from the year 2000 that report results separately for people with a diagnosis of schizophrenia, schizoaffective disorder, schizophreniform disorder or first episode schizophrenia. Reviews were identified by searching the databases MEDLINE, EMBASE, CINAHL, Current Contents, PsycINFO and the Cochrane library. Hand searching reference lists of identified reviews was also conducted. When multiple copies of reviews were found, only the most recent version was included. Reviews with pooled data are given priority 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 rated as having 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 or if there is a dose dependent response. We have also taken into account sample size and whether results are 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 four systematic reviews that met our inclusion criteria[3-6].

- Moderate to high quality evidence finds a large effect of more autistic symptoms in people with schizophrenia compared to controls and a large effect of fewer autistic symptoms in people with schizophrenia



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compared to people with an autistic spectrum disorder.

- Moderate to high quality evidence finds the prevalence rate of schizophrenia spectrum disorders in adults with an autism spectrum disorder is around 9.5%. In people with autism and an IQ over 70, the prevalence rate is lower, around 6.4%.
- Moderate quality evidence finds a significant, medium-sized effect of increased risk of schizophrenia in people with an autism spectrum disorder compared to people without an autism spectrum disorder.



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*De Crescenzo F, Postorino V, Siracusano M, Riccioni A, Armando M, Curatolo P, Mazzone L*

## Autistic symptoms in schizophrenia spectrum disorders: A systematic review and meta-analysis

**Frontiers in Psychiatry 2019; 10: 78**

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| | |
|---|---|
| **Comparison** | **Assessment of autism symptoms in people with schizophrenia vs. controls and vs. people with an autistic spectrum disorder.** |
| **Summary of evidence** | **Moderate to high quality evidence (large sample, inconsistent, precise, direct) finds a large effect of more autistic symptoms in people with schizophrenia compared to controls and a large effect of fewer autistic symptoms in people with schizophrenia compared to people with an autistic spectrum disorder.** |
| **Schizophrenia spectrum disorders** | |
| *A large effect showed people with schizophrenia have more autistic symptoms than controls;*<br>11 studies, N = 1,226, SMD = 1.39, 95%CI 1.11 to 1.68, $p < 0.0001$, $I^2 = 73\%$<br>The effect size was large and significant on all Autism-Spectrum Quotient subscales (social, attention, communication, and imagination) except the attention to detail subscale.<br>*A large effect showed people with schizophrenia have fewer autistic symptoms than people with an autism spectrum disorder;*<br>8 studies, N = 553, SMD = -1.27, 95%CI -1.77 to -0.76, $p < 0.0001$, $I^2 = 84\%$<br>The effect size was medium to large and significant in all Autism-Spectrum Quotient subscales (social, attention, communication, imagination, and attention to detail).<br>Results were similar in subgroup analyses of children < 18 years and adults > 18 years. | |
| **Consistency in results**‡ | Inconsistent |
| **Precision in results**§ | Precise |
| **Directness of results**‖ | Direct |

*De Giorgi R, De Crescenzo F, D'Alo GL, Pesci NR, Di Franco D, Sandini C, Armando M*

## Prevalence of non-affective psychoses in individuals with autism spectrum disorders: A systematic review

**Journal of Clinical Medicine 2019; 8: 1304**

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| | |
|---|---|
| **Comparison** | **The prevalence of schizophrenia in people with an autism spectrum disorder.** |
| **Summary of evidence** | **Moderate quality evidence (large sample, inconsistent, imprecise, direct) suggests the prevalence rate of schizophrenia spectrum disorders in adults with an autism spectrum disorder is around 9.5%.** |
| **Schizophrenia spectrum disorders** | |
| 14 studies, N = 1,708, prevalence = 9.5%, 95%CI 2.6% to 16.0%<br>Subgroup analyses showed higher prevalence of non-affective psychoses among inpatients than outpatients with an autism spectrum disorder, when operationalised criteria were used, and in studies with smaller sample sizes. Rates were similar in children and adults. | |
| **Consistency in results** | Authors report data are inconsistent. |
| **Precision in results** | Appears imprecise |
| **Directness of results** | Direct |

*Lugo Marin J, Alviani Rodriguez-Franco M, Mahtani Chugani V, Magan Maganto M, Diez Villoria E, Canal Bedia R*

## Prevalence of Schizophrenia Spectrum Disorders in Average-IQ Adults with Autism Spectrum Disorders: A Meta-analysis

**Journal of Autism and Developmental Disorders 2018; 48: 239-50**

| View review abstract online | |
|---|---|
| **Comparison** | **The prevalence of schizophrenia in adults with an autism spectrum disorder and an IQ over 70.** |
| **Summary of evidence** | **Moderate to high quality evidence (large sample, inconsistent, appears precise, direct) suggests the prevalence rate of schizophrenia spectrum disorders in adults with an autism spectrum disorder and an IQ over 70 is around 6.4%.** |
| **Schizophrenia spectrum disorders** | |
| *The prevalence rate of schizophrenia spectrum disorders is around 6.4%;* 10 studies, N = 713, event rate = 0.064, 95%CI 0.040 to 0.101, $p < 0.05$, $I^2 = 49\%$ | |
| **Consistency in results** | Inconsistent |
| **Precision in results** | Appears precise |
| **Directness of results** | Direct |

*Zheng Z, Zheng P, Zou X*

## Association between schizophrenia and autism spectrum disorder: A systematic review and meta-analysis

**Autism Research 2018; 11: 1110-9**

View review abstract online

| **Comparison** | **Rates of schizophrenia in people an autism spectrum disorder vs. people without an autism spectrum disorder.** |
|---|---|
| **Summary of evidence** | **Moderate quality evidence (large sample, inconsistent, imprecise, direct) suggests a significant, medium-sized increased risk of schizophrenia in people with an autism spectrum disorder.** |
| **Schizophrenia diagnosis** | |

# TECHNICAL COMMENTARY

## Autism spectrum disorders

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| *A significant, medium-sized effect of increased rates of schizophrenia in people with an autism spectrum disorder;*<br>10 studies, N = 1,965,058, OR = 3.55, 95%CI 2.08 to 6.05, $p < 0.001$, $I^2 = 76\%$<br>Subgroup analysis showed the three case control studies reported a significantly higher pooled OR than the seven cross-sectional studies (OR = 8.20 vs. OR = 2.47).<br>There were no moderating effects of diagnosis (autism vs. autism spectrum), study location (US vs. Europe) or whether study results were adjusted for confounding factors. |

| | |
|---|---|
| **Consistency in results** | Inconsistent |
| **Precision in results** | Imprecise |
| **Directness of results** | Direct |

## Explanation of acronyms

CI = confidence interval, $I^2$ = the percentage of the variability in effect estimates that is due to heterogeneity rather than sampling error (chance), N = number of participants, OR = odds ratio, *p* = statistical probability of obtaining that result ($p < 0.05$ generally regarded as significant), vs. = versus



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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[7].

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† Different effect measures are reported by different reviews.

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

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

Weighted mean difference scores refer to mean differences between treatment and comparison groups after treatment (or occasionally pre to post treatment) and in a randomised trial there is an assumption that both groups are comparable on this measure prior to treatment. Standardised mean differences are divided by the pooled standard deviation (or the standard deviation of one group when groups are homogenous) 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[7].

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



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groups. A medium effect is considered if RR > 2 or < 0.5 and a large effect if RR > 5 or < 0.2[8]. 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. Unstandardised (*b*) regression coefficients indicate the average change in the dependent variable associated with a 1 unit change in the independent variable, statistically controlling for the other independent variables. Standardised regression coefficients represent the change being in units of standard deviations to allow comparison across different scales.

‡ Inconsistency refers to differing estimates of effect across studies (i.e. heterogeneity or variability in results) that is not explained by subgroup analyses and therefore reduces confidence in the effect estimate. $I^2$ is the percentage of the variability in effect estimates that is due to heterogeneity rather than sampling error (chance) - 0% to 40%: heterogeneity might not be important, 30% to 60%: may represent moderate heterogeneity, 50% to 90%: may represent considerable heterogeneity and over this is considerable heterogeneity. $I^2$ can be calculated from Q (chi-square) for the test of heterogeneity with the following formula[7];

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

§ 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[9].

‖ 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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