TECHNICAL COMMENTARY

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SCHIZOPHRENIA LIBRARY

Psychopathology in relatives

Introduction

Due to the significant genetic loading of schizophrenia, first-degree relatives may also show signs of psychopathology. This could include schizophrenia, bipolar disorder or other mental illnesses.

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[1]) 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[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 two systematic reviews that met our inclusion criteria[3, 4].

- Moderate to high quality evidence finds no significant increases in anxiety disorders in offspring of people with schizophrenia.
- Moderate to low quality evidence finds no significant increases in disruptive behavioural disorders in offspring of people with schizophrenia.

Margarete Ainsworth Building, Barker Street, Randwick NSW 2031. Phone: 02 9399 1000. Email: info@neura.edu.au

Ayano G, Betts K, Maravilla JC, Alati R

A Systematic Review and Meta-Analysis of the Risk of Disruptive Behavioral Disorders in the Offspring of Parents with Severe Psychiatric Disorders

Child Psychiatry and Human Development 2021; 52: 77-95

View review abstract online

Comparison	**Rates of disruptive behavioural disorders in offspring of people with schizophrenia vs. controls.**
Summary of evidence	**Moderate to low quality evidence (unclear sample sizes, inconsistent, imprecise, direct) finds no significant increases in disruptive behavioural disorders in offspring of people with schizophrenia.**
Disruptive behavioural disorders	
No significant differences between groups; Disruptive behavioural disorder: 2 studies, N not reported RR = 2.41, 95%CI 0.72 to 8.05, $p > 0.05$, $I^2 = 68\%$ Oppositional defiant disorder: 1 study, N not reported, RR = 1.33, 95%CI 0.46 to 3.85, $p > 0.05$ Conduct disorder: 1 study, N not reported, RR = 2.20, 95%CI 0.45 to 10.63, $p > 0.05$	
Consistency‡	Inconsistent where applicable
Precision§	Imprecise
Directness‖	Direct

Ayano G, Betts K, Maravilla JC, Alati R

The risk of anxiety disorders in children of parents with severe psychiatric disorders: a systematic review and meta-analysis

Journal of Affective Disorders 2021; 282: 472-87

View review abstract online

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Comparison	**Rates of anxiety disorders in offspring of parents with schizophrenia vs. controls.**
Summary of evidence	**Moderate to high quality evidence (large sample, consistent, imprecise, direct) finds no significant increases in anxiety disorders in offspring of people with schizophrenia.**
Anxiety disorders	
No significant differences between groups; Any anxiety disorder: 5 studies, N = 1,233, RR = 1.36, 95%CI 0.87 to 2.13, $p > 0.05$, $I^2 = 45\%$, $p = 0.107$ Obsessive-compulsive disorder: 2 studies, N not reported, RR = 1.79, 95%CI 0.64 to 5.04, $p > 0.05$, $I^2 = 0\%$ Separation anxiety disorder: 1 study, N not reported, RR = 1.79, 95%CI 0.64 to 5.04, $p > 0.05$ Panic disorder: 1 study, N not reported, RR = 3.24, 95%CI 0.61 to 17.29, $p > 0.05$ Social phobia: 1 study, N not reported, RR = 1.71, 95%CI 0.28 to 4.89, $p > 0.05$	
Consistency	Consistent where applicable.
Precision	Imprecise
Directness	Direct

Explanation of acronyms

CI = confidence interval, N = number of participants, I^2 = the percentage of the variability in effect estimates that is due to heterogeneity rather than sampling error (chance), N = sample size, p = statistical probability of obtaining that result ($p < 0.05$ generally regarded as significant), RR = risk ratio, 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[5].

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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. Standardized 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. 0.2 represents a small effect, 0.5 a moderate effect, and 0.8 and over represents a large effect[5].

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[6]. lnOR stands for logarithmic OR where a lnOR of 0 shows no difference between groups. Hazard ratios measure the effect of an explanatory variable on the hazard or risk of an event.

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

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between variables. They 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[5];

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

§ 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[7].

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

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References

1. Moher D, Liberati A, Tetzlaff J, Altman DG, PRISMAGroup (2009): Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *British Medical Journal* 151: 264-9.
2. GRADEWorkingGroup (2004): Grading quality of evidence and strength of recommendations. *British Medical Journal* 328: 1490.
3. Ayano G, Betts K, Maravilla JC, Alati R (2021): A Systematic Review and Meta-Analysis of the Risk of Disruptive Behavioral Disorders in the Offspring of Parents with Severe Psychiatric Disorders. *Child psychiatry and human development* 52: 77-95.
4. Ayano G, Betts K, Maravilla JC, Alati R (2021): The risk of anxiety disorders in children of parents with severe psychiatric disorders: a systematic review and meta-analysis. *Journal of Affective Disorders* 282: 472-87.
5. CochraneCollaboration (2008): Cochrane Handbook for Systematic Reviews of Interventions. Accessed 24/06/2011.
6. Rosenthal JA (1996): Qualitative Descriptors of Strength of Association and Effect Size. *Journal of Social Service Research* 21: 37-59.
7. GRADEpro (2008): [Computer program]. Jan Brozek, Andrew Oxman, Holger Schünemann. *Version 32 for Windows*