TECHNICAL COMMENTARY

Genetic and non-genetic risk

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Introduction

Many disorders are the result of interaction between susceptibility genes and environmental influences. One example is cardiovascular disease – those with a family history of this disease are more susceptible to heart attack and environmental influences such as diet can increase the risk. Schizophrenia is also a complex disorder that appears to be linked to both genetic and environmental influences.

Quantitative statistical genetics is a method which can be used to estimate how much of the variation in a trait, such as symptoms of schizophrenia, is related to genetic or environmental factors. In the commonly used twin model study design, identical twins are assumed to share 100% of their genetic material, and dizygotic twins to share 50%; both types of twins are assumed to have been reared in identical environments. By comparing the degree of similarity for a trait between the monozygotic and dizygotic twins, the amount of variation due to genetic, shared environment, or unique environment can be derived. Twin studies relevant to a disorder can include twin pairs in which only one twin has the condition, pairs where both are affected, or twins who have traits relevant to the disorder without meeting criteria for the condition itself. Other study designs besides twins can be used to examine the degree to which genetic and environmental factors contribute to variation in a trait. Extended pedigrees in which the degree of genetic relatedness is known can also estimate genetic contributions to variation, while adoption studies can determine whether parental effects are due to genes or to the rearing environment.

Genome-wide association studies have identified multiple genes associated with increase risk, but each has only small effects. These can be collapsed into a single polygenic risk score in the hope of quantifying the individual degree of genetic risk for schizophrenia.

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 seven systematic reviews that met our inclusion criteria[3-9].

- Moderate quality suggests genetic effects contributing to risk of schizophrenia is much higher than environmental effects.
- Moderate to high quality evidence found large increased risk of schizophrenia in people with one or two first-degree relatives with schizophrenia compared to people without a relative with schizophrenia.
- Moderate to low quality evidence suggests a large risk of developing schizophrenia in the offspring of parents with schizophrenia compared to controls. There is no increased risk of depression, anxiety, disruptive disorders, substance use disorders, or attention deficit hyperactivity disorder (ADHD) in the offspring of parents with schizophrenia.

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- Moderate quality evidence suggests familial factors (genetic and shared environment) contribute around 63% to the variance in general cognitive ability of people with schizophrenia and their family members.
- Moderate to low quality evidence suggests a medium-sized increase in prevalence of subclinical psychotic symptoms in people with a family history of any mental illness.
- Moderate to low quality evidence suggests high familial coaggregation of schizophrenia and bipolar disorder, with first-degree relatives of patients with schizophrenia or bipolar showing an increased risk of developing either disorder.
- Moderate quality evidence suggests schizophrenia polygenic risk scores are associated with increased symptoms of schizophrenia, particularly negative and disorganised symptoms.

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Blokland GAM, Mesholam-Gately RI, Toulopoulou T, Del Re EC, Lam M, DeLisi LE, Donohoe G, Walters JTR, Genus Consortium Seidman LJ, Petryshen TL

Heritability of Neuropsychological Measures in Schizophrenia and Nonpsychiatric Populations: A Systematic Review and Meta-analysis

Schizophrenia Bulletin 2017; 43: 788-800

View review abstract online

Comparison	**Heritability of cognitive symptoms in people with schizophrenia.**
Summary of evidence	**Moderate quality evidence (large samples, unable to assess consistency, some imprecision, direct) suggests familial factors (genetic and shared environment) contribute around 63% of the variance in general cognitive ability.**
Heritability of cognitive symptoms	
General cognitive ability: 5 family studies, N = 2,139, h^2 = 63%, 95%CI 45% to 81% Verbal ability: 8 family studies, N = 5,102, h^2 = 55%, 95%CI 44% to 66% Visuospatial ability: 7 family studies, N = 4,912, h^2 = 51%, 95%CI 46% to 55% Verbal memory: 9 family studies, N = 4,757, h^2 = 44%, 95%CI 36% to 52% Working memory: 10 family studies, N = 6,131, h^2 = 43%, 95%CI 38% to 47% Motor ability: 4 family studies, N = 1,443, h^2 = 39%, 95%CI 37% to 40% Non-verbal memory: 7 family studies, N = 4,773, h^2 = 38%, 95%CI 32% to 44% Attention/vigilance: 6 family studies, N = 3,566, h^2 = 29%, 95%CI 20% to 37% Attention/processing speed: 9 family studies, N = 3,947, h^2 = 26%, 95%CI 18% to 34% Social cognition: 3 family studies, N = 2,879, h^2 = 25%, 95%CI 17% to 32% Executive functioning: 8 family studies, N = 7,627, h^2 = 20%, 95%CI 13% to 27% Authors report these heritability statistics are similar in non-psychiatric family studies.	
Consistency in results‡	Unable to assess; no measure of consistency is reported
Precision in results§	Some imprecision
Directness of results‖	Direct

Lo L, Kaur R, Meiser B, Green M

Risk of schizophrenia in relatives of individuals affected by schizophrenia: A meta-analysis

Psychiatry Research 2020; 286: 112852

View review abstract online

Comparison	**Risk of schizophrenia in first-degree relatives of people with schizophrenia vs. controls.**
Summary of evidence	**Moderate to high quality evidence (large sample, consistent, imprecise, direct) found large increased risk of schizophrenia in people with one or two first-degree relatives with schizophrenia compared to people without a relative with schizophrenia.**
Schizophrenia	
Large effects showed increased risk of schizophrenia in people with one or two first-degree relatives with schizophrenia; One or two probands: 19 studies, N = 9,945, OR = 7.80, 95%CI 5.22 to 11.63, $p < 0.0001$, $I^2 = 0\%$ One proband: 17 studies, N not reported, OR = 7.69, 95%CI 5.11 to 11.56, $I^2 = 0\%$ Two probands: 2 studies, N not reported, OR = 11.11, 95%CI 1.45 to 85.02	
Consistency in results	Consistent
Precision in results	Imprecise
Directness of results	Direct

Linscott RJ, van Os J

An updated and conservative systematic review and meta-analysis of epidemiological evidence on psychotic experiences in children and adults: on the pathway from proneness to persistence to dimensional expression across mental disorders

Psychological Medicine 2013; 43: 1133-1149

View review abstract online

Comparison	**Prevalence and incidence of subclinical psychotic symptoms in people with vs. without a family history of mental illness.**
Summary of evidence	**Moderate to low quality evidence (unclear sample sizes, inconsistent, imprecise, direct) suggests a medium-sized increase in rates of subclinical psychotic symptoms in people with a family history of mental illness.**
Subclinical psychotic symptoms	
Significant, medium increased rate of subclinical psychotic symptoms in people with a family history of mental illness; 4 studies, N not reported, OR = 3.06, 95%CI 1.58 to 5.94, $p < 0.05$, $I^2 = 81\%$, $p < 0.01$	
Consistency in results	Inconsistent
Precision in results	Imprecise
Directness of results	Direct

Mistry S, Harrison JR, Smith DJ, Escott-Price V, Zammit S

The use of polygenic risk scores to identify phenotypes associated with genetic risk of schizophrenia: Systematic review

Schizophrenia Research 2018; 197: 2-8

View review abstract online

Comparison	**Association between polygenic risk scores for schizophrenia (SZ-PRS) and symptoms of schizophrenia and other disorders.**
Summary of evidence	**Moderate quality evidence (large samples, appears inconsistent, unable to assess precision, direct) suggests SZ-PRS are associated with increased symptoms of schizophrenia, particularly negative and disorganised symptoms.**
Schizophrenia symptoms and severity	
1 study (N = 2,454) found SZ-PRS was significantly associated with negative and disorganised symptom scores, but not positive or mood symptom scores in people with schizophrenia. 1 study (N = 462) found SZ-PRS was significantly associated with positive, negative and disorganised symptom scores in both cases with schizophrenia and controls without schizophrenia. It was also significantly associated with mania and depression scores. 1 study (N = 2,133) found SZ-PRS was significantly associated with negative symptom scores, but	

not positive symptom scores in general population adolescents. 1 study (N = 5,444) found SZ-PRS was significantly associated with negative symptoms and anxiety, but not with depression or positive symptoms in adolescents. 1 study (N = 3,907) found conflicting results of both increased and decreased associations between SZ-PRS and psychotic-like experiences in adolescents. 1 study (N = 804) found higher SZ-PRS scores in people with schizophrenia with a history of clozapine treatment compared to those without, as well as in those who responded to clozapine compared to those who did not. 1 study (N = 83) found no association between SZ-PRS and antipsychotic dosage or global assessment of functioning.	
Consistency in results	Appears inconsistent
Precision in results	Unable to assess; no CIs are reported.
Directness of results	Direct

Rasic D, Hajek T, Alda M, Uher R

Risk of Mental Illness in Offspring of Parents With Schizophrenia, Bipolar Disorder, and Major Depressive Disorder: A Meta-Analysis of Family High-Risk Studies

Schizophrenia Bulletin 2014; 40(1): 28-38

View review abstract online

Comparison	**Risk of developing schizophrenia or other severe mental disorders in offspring of parents with schizophrenia vs. controls who do not have a parent with schizophrenia. Controls were matched on demographic variables.**
Summary of evidence	**Moderate to low quality evidence (unclear sample sizes, inconsistent, imprecise, direct) suggests a large increased risk of developing schizophrenia in the offspring of parents with schizophrenia compared to controls. No significant effect of increased risk of bipolar, depression, anxiety, disruptive disorders, substance use disorder or ADHD in the offspring of parents with schizophrenia.**
Schizophrenia or other severe mental disorder	

Large, significant effect of increased risk of schizophrenia in the offspring of a parent with schizophrenia compared to controls; Risk of developing schizophrenia: RR = 7.54, 95%CI 4.02 to 14.13, *p* = 0.000 *Small, significant effect of increased risk of any severe mental disorder in the offspring of a parent with schizophrenia compared to controls;* Risk of developing any disorder: RR = 1.45, 95%CI 1.17 to 1.79, *p* = 0.001 *No significant effect of increased risk of bipolar, depression, anxiety, disruptive disorders, substance use disorder or ADHD in the offspring of a parent with schizophrenia compared to controls;* Risk of developing bipolar disorder: RR = 1.84, 95%CI 0.73 to 4.66, *p* = 0.197 Risk of developing depression: RR = 1.31, 95%CI 0.78 to 2.20, *p* = 0.312 Risk of developing anxiety: RR = 0.97, 95%CI 0.68 to 1.39, *p* = 0.874 Risk of developing disruptive disorders: RR = 1.90, 95%CI 0.81 to 4.49, *p* = 0.142 Risk of developing substance use disorder: RR 1.72, 95%CI 0.88 to 3.37, *p* = 0.112 Risk of developing ADHD: RR = 1.76, 95%CI 0.34 to 9.03, *p* = 0.500 The risk of developing schizophrenia in offspring of a parent with bipolar disorder or depression was not significantly different to controls. Results did not change significantly in subgroup/regression analyses of publication year, age, region of study origin, assessor blinding, duration of follow-up, type of control group, and the number of follow-up assessments.

Consistency in results	Consistency measures were not reported; authors state the results were not consistent.
Precision in results	Imprecise
Directness of results	Direct

Sullivan PF, Kendler KS, Neale MC

Schizophrenia as a complex trait: evidence from a meta-analysis of twin studies

Archives of General Psychiatry 2003; 60(12): 1187-1192

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Comparison	**Differences between genetic effects and environmental effects for risk of schizophrenia corrected for ascertainment.**

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Summary of evidence	**Moderate quality evidence (unclear sample sizes, inconsistent, precise, direct) suggests that genetic effects contributing to risk of schizophrenia is much higher than environmental effects.**
Genetic and environmental risk of schizophrenia	
12 observational twin studies, 4 blinded to zygosity and co-twin status, N = unclear; Random population ascertainment (2 studies) = all 4 types of twin pairs - concordant unaffected twin pairs, the 2 discordant twin pairs (one has the disorder the other doesn't), and concordant affected twin pairs (representative of the population so no ascertainment correction necessary). Complete ascertainment (4 studies) = concordant unaffected twin pairs are the only pairs not observed, so that concordant and discordant affected twins are ascertained. Single ascertainment (2 studies) = only 1 of the 2 possible discordant cells is observed together with concordant affected pairs. Incomplete ascertainment (4 studies) = intermediate between complete and single ascertainment. *Results suggest the presence of both additive genetic and common environmental effects, with substantial additive genetic effects;* The point estimate of heritability in genetic liability to schizophrenia = 81%, 95% CI, 73% to 90% Estimated common or shared environmental effects = 11%, 95% CI 3% to 19%, I^2 = 82%, $p < 0.001$ The summary estimate for monozygotic twins = r_{MZ}=0.92; 95% CI = 0.91 to 0.94 The summary estimate for dizygotic twins = r_{DZ}=0.52; 95% CI = 0.48 to 0.56	
Subgroup analysis to compare results from superior studies (4 studies) with inferior studies (8 studies); Similar estimates for additive genetic effects (77% vs. 78%) Authors state that because prevalence can influence the variance component estimates and studies varied in their population prevalence estimates (drawn from various regions), all studies were forced to have a population prevalence for schizophrenia of 0.5%, 0.75%, and 1% which resulted in similar pattern of results.	
Consistency in results	Inconsistent
Precision in results	Precise
Directness of results	Direct

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Van Snellenberg J, de Candia T

Meta-analytic evidence for familial coaggregation of schizophrenia and bipolar disorder

Archives of General Psychiatry 2009; 66(7): 748-755

View review abstract online

Comparison	**Assessment of the existence of schizophrenia or bipolar disorder diagnoses within the same family.**
Summary of evidence	**Moderate to low quality evidence (unclear sample size, unable to assess precision or consistency, direct) suggests high familial coaggregation of schizophrenia and bipolar disorder, with first-degree relatives of patients with schizophrenia or bipolar showing an increased risk of developing either disorder.**
Schizophrenia or bipolar disorder	
Schizophrenia The risk of schizophrenia in relatives of a person with schizophrenia was 6.68%, compared to 0.85% in controls, OR = 8.38, p = 0.001. The risk of schizophrenia in relatives of a person with bipolar was 1.77%, compared to 0.85% in controls, OR = 2.10, p = 0.06. *Bipolar disorder* The risk of bipolar disorder in relatives of a person with bipolar was 10.54%, compared to 0.48% in controls, OR = 24.47, p = 0.001. The risk of bipolar disorder in relatives of a person with schizophrenia was 0.99%, compared to 0.48% in controls, OR = 2.08, p = 0.01.	
Consistency	Unable to assess; no measure of consistency is reported.
Precision	Unable to assess; no measure of precision is reported.
Directness	Direct

Explanation of acronyms

ADHD = attention deficit hyperactivity disorder, CI = confidence interval, dz = dizygotic, h^2 = heritability index, I^2 = the percentage of the variability in effect estimates that is due to heterogeneity rather than sampling error (chance), mz = monozygotic, N = number of participants, OR = odds ratio, *p* = statistical probability of obtaining that result ($p < 0.05$ generally regarded as significant), Q = Q statistic (chi-square) for the test of heterogeneity, *r* = correlation, RR = risk ratio, SZ-PRS = schizophrenia polygenic risk scores, 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; 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.

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† Different effect measures are reported by different reviews.

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

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. 0.2 represents a small effect, 0.5 a medium effect, and 0.8 and over represents a large treatment 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

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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.

‡ Inconsistency refers to differing estimates of treatment 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 substantial heterogeneity and 75% to 100%: considerable heterogeneity. I^2 can be calculated from Q (chi-square) for the test of heterogeneity with the following formula;

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

§ 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, this 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 so is 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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