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Parental psychological factors

Introduction

Exposure to maternal psychological factors such as stress, depression, or psychosis during pregnancy, may be linked to risk of schizophrenia in the offspring. The mechanisms by which these factors influence risk of schizophrenia is unclear, however genetic predisposition and/or inflammatory processes caused by stress may be involved.

Method

We have included only systematic reviews 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 one systematic review that met our inclusion criteria[3].

- Moderate to low quality evidence suggests medium-sized effects of increased risk of schizophrenia spectrum or non-affective psychoses following exposure to any parental psychopathology or overall maternal stress during pregnancy. Risk was highest with exposure to maternal psychosis. There were no associations with death of a close relative or exposure to other catastrophic events (unspecified) during pregnancy.

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Davies C, Segre G, Estrade A, Radua J, De Micheli A, Provenzani U, Oliver D, Salazar de Pablo G, Ramella-Cravaro V, Besozzi M, Dazzan P, Miele M, Caputo G, Spallarossa C, Crossland G, Ilyas A, Spada G, Politi P, Murray RM, McGuire P, Fusar-Poli P

Prenatal and perinatal risk and protective factors for psychosis: a systematic review and meta-analysis

The Lancet Psychiatry 2020; 7: 399-410

View review abstract online

Comparison	**Risk of psychotic disorders (mostly schizophrenia spectrum or non-affective psychosis) in adulthood in people who were exposed to parental psychopathology vs. controls.**
Summary of evidence	**Moderate to low quality evidence (unclear sample size, mostly inconsistent and imprecise, direct) suggests medium-sized effects of increased risk of psychotic disorders following exposure to any parental psychopathology or overall maternal stress during pregnancy. Risk was highest with exposure to maternal psychosis. There was no association with death of a close relative or exposure to other catastrophic events (unspecified).**

Parental psychopathology

Medium-sized, significant increased risk of psychotic disorders following exposure to;

Any maternal psychopathology: 9 studies, N not reported, OR = 4.60, 95%CI 2.74 to 7.73, $p < 0.0001$, $I^2 = 97\%$, $p < 0.0001$

Any paternal psychopathology: 5 studies, N not reported, OR = 2.73, 95%CI 2.33 to 3.19, $p < 0.0001$, $I^2 = 27\%$, $p = 0.24$

Maternal affective disorder: 3 studies, N not reported, OR = 2.26, 95%CI 1.09 to 4.70, $p = 0.029$, $I^2 = 90\%$, $p < 0.0001$

Large, significant increased risk of psychotic disorders following exposure to maternal psychosis;

6 studies, N not reported, OR = 7.61, 95%CI 6.29 to 9.21, $p < 0.0001$, $I^2 = 62\%$, $p = 0.021$

Maternal stress during pregnancy

A medium-sized, significant increased risk of psychotic disorders with exposure to any maternal stress during pregnancy (not specified);

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4 studies, N not reported, OR = 2.40, 95%CI 1.15 to 5.01, p = 0.019, I^2 = 80%, p = 0.017 After excluding studies using retrospective recall, this result was no longer significant. *No significant effects of;* Death or severe illness of a close relative: 3 studies, N not reported, OR = 0.84, 95%CI 0.61 to 1.17, p = 0.31, I^2 = 0%, p = 0.45 Catastrophic events: 5 studies, N not reported, OR = 1.15, 95%CI 0.98 to 1.36, p = 0.08, I^2 = 74%, p = 0.0017 Subgroup analyses of trimesters separately give similar results for catastrophic events.	
Consistency in results‡	Inconsistent, apart from any paternal psychopathology and death of a relative
Precision in results§	Imprecise, apart from catastrophic event
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[4].

† 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. 0.2 represents a small effect, 0.5 a medium effect, and 0.8 and over represents a large effect[4].

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[5]. lnOR stands for logarithmic OR where a lnOR of 0 shows no difference between groups. Hazard ratios

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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[4];

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

§ 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[6].

‖ 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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