TECHNICAL COMMENTARY

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Maternal illness during pregnancy

Introduction

Maternal illness during pregnancy with diabetes, Toxoplasma gondii, rubella, cytomegalovirus, herpes simplex virus and other microbes have been associated with brain and behavioural abnormalities in the offspring, and so have been investigated as possible risk factors for schizophrenia.

Cytokine and c-reactive protein alterations have been found in people with schizophrenia. C-reactive protein is a frequently used marker of systemic inflammation, and cytokines act to regulate immunological and inflammatory responses to pathogens. Increases in maternal c-reactive protein and cytokines during pregnancy may lead to alterations in neurodevelopment in the foetus.

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. Due to the high volume of systematic reviews we have now limited inclusion to systematic meta-analyses. Where no systematic meta-analysis exists for a topic, systematic reviews without meta-analysis are included for that topic. 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.

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 with 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, there is a dose dependent response or if results are reasonably 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 suggests a large association between risk of schizophrenia and exposure to maternal diabetes in utero, with no association with maternal urinary tract infections.

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- Moderate to low quality evidence suggests medium-sized effects of increased risk of schizophrenia with exposure to maternal infections in utero, particularly upper respiratory tract, genital or reproductive infections, also herpes simplex virus and Toxoplasma gondii, but not influenza.
- High quality evidence suggests a small effect of increased risk of schizophrenia in the offspring of women with increased c-reactive protein levels during pregnancy.
- Moderate to high quality evidence suggests small effects of increased risk of schizophrenia in the offspring of women with increased IL-8 or IL-10 during pregnancy.

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Cannon M, Jones PB, Murray RM

Obstetric complications and schizophrenia: historical and meta-analytic review

American Journal of Psychiatry 2002; 159(7): 1080-1092

View review abstract online

Comparison	**Association between obstetric complications and schizophrenia, not controlling for possible confounding factors (eg other prenatal influences).**
Summary of evidence	**Moderate to high quality evidence (large samples, consistent, imprecise, direct) suggests a large association between increased odds of schizophrenia and exposure to maternal diabetes in utero. There was no association with urinary tract infections.**
Maternal diabetes during pregnancy	
Significant, large increase in odds of schizophrenia in the offspring; 2 studies, N = 2,146, OR = 7.76, 95%CI 1.37 to 43.90, $p < 0.03$	
Urinary tract infections during pregnancy	
No significant increase in odds of schizophrenia in the offspring; 3 studies, N = 508,420, OR = 0.86, 95%CI 0.48 to 1.55, $p = 0.63$	
Consistency in results‡	Authors state the data are consistent.
Precision in results§	Imprecise
Directness of results‖	Direct

Khandaker G, Zimbron J, Dalman C, Lewis G, Jones P

Prenatal maternal infection, neurodevelopment and adult schizophrenia: a systematic review of population based studies

Psychological Medicine 2013; 43(2): 239-257

Maternal illness during pregnancy

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Comparison	**Exposure to prenatal maternal infections in adults with schizophrenia vs. population controls.**
Summary of evidence	**Moderate to low quality evidence (large samples, unable to assess consistency or precision, indirect,) suggests a medium sized increased risk of schizophrenia following exposure to maternal infections in utero, particularly upper respiratory tract, genital or reproductive infections, also herpes simplex virus, and Toxoplasma gondii.**
Prenatal maternal infections	

Serum assays

Herpes simplex virus (HSV);

3/5 studies (N = 1,200) reported a significant increased risk of schizophrenia (~ 50%) after exposure to HSV-2 infection during pregnancy. 1 study (N = 110) reported a non-significant, 30% increase in risk of schizophrenia spectrum disorder following HSV-2 exposure, and 1 study (N = 648) reported no increase in risk of schizophrenia following HSV-1 or HSV-2 exposure.

Toxoplasma Gondii;

2 studies (N = 771) reported significant increased risk of schizophrenia (ORs 1.79 and 2.61) after exposure to elevated levels of maternal IgG antibodies to T. gondii. One study found no association between T. gondii exposure and non-affective psychosis but was limited by a very small sample of psychosis (N = 40).

Influenza;

2 studies (N = 372) reported increased risk of schizophrenia after exposure to influenza, but neither study reported significant differences compared to controls.

Clinically diagnosed infections

General infections;

1 study (N = 1,119,474) reported maternal hospitalisation for any infection during second trimester of pregnancy was associated with increased risk of schizophrenia in offspring (RR 1.72, 95% CI 1.15 to 2.46). 1 study (N = 7,941) reported bacterial infection during the first trimester was reported to be associated with a twofold increased risk of schizophrenia at follow-up at both age 34 and 47 years. Risk was also increased, but not statistically significant for second trimester exposure. No significant increase in risk after prenatal exposure to viral infections.

Respiratory infection;

2 studies (N = 16,964) reported that maternal upper respiratory tract infection during the second trimester was reported to be associated with a two to threefold increased risk of schizophrenia in adult offspring by age 47 years.

Genital, reproductive and urinary infection;

3/4 studies reported increased risk of schizophrenia following exposure to infections, mostly during

the early stages of gestation. 1 study (N = 7,794) reported that maternal genital or reproductive infection during the peri-conceptional period (30 days before and after the last menstrual period) was associated with a fivefold increased risk schizophrenia in adult offspring, with no increase in risk during pregnancy. 1 study (N = 1,119,474) reported that hospital admission for genital infection during pregnancy was associated with a twofold increased risk of schizophrenia in adult offspring. 1 study (N = 7,941) reported that maternal gonococcal infection during pregnancy was associated with a threefold increased risk of schizophrenia by age 47 years. 1 study (N = 23,404) reported no association between maternal hospitalization with pyelonephritis during pregnancy and risk of schizophrenia in the offspring. *Interaction between prenatal maternal infection and other risk factors;* 1 study (N = 23,404) reported a fivefold increased risk of schizophrenia in offspring exposed to maternal pyelonephritis during pregnancy who also have a family history of schizophrenia. 1 study (N = 744) reported that mother's sexual behaviour prior to and during pregnancy was relevant to HSV-2 seropositivity and subsequent increased risk of schizophrenia. 6 studies (N = 532) reported that exposure to maternal infection or increased inflammatory cytokines during pregnancy were associated with significant deficits in executive functioning, childhood and adult verbal IQ, and greater IQ decline during the pre-morbid period and increased ventricular volume, increased length of the cavum septum pallucidum, and reduced cortical volume in offspring who developed schizophrenia.	
Consistency in results	Unable to assess; no measure of consistency is reported.
Precision in results	Unable to assess; no CIs are reported.
Directness of results	Indirect – exposure inferred through maternal infection.

Selten J-P, Frissen A, Lensvelt-Mulders G, Morgan VA

Schizophrenia and 1957 Pandemic of Influenza: Meta-analysis

Schizophrenia Bulletin 2010; 36(2): 219-228

View review abstract online

Comparison 1	**The number of cases of schizophrenia among people born after the 1957 influenza pandemic compared to the number of cases of schizophrenia among people born in surrounding years (between 1 and 6 years on either side of 1957). Studies considered infants born in the first month after the peak as having been exposed during the ninth month of pregnancy and classified the other months accordingly to assess first, second and third trimester exposure.**
Summary of evidence	**Moderate quality evidence (large samples, precise, some inconsistency, indirect) suggests no association between**

	exposure to influenza during pregnancy and risk of schizophrenia in the offspring.
Studies conducted in the United States, Europe, and Australia where 1957 pandemic came in one wave and where approximately 50% of the population reported having had influenza	
6 population-level studies *No significant differences in the number of cases of schizophrenia between people potentially exposed to influenza prenatally and those potentially not exposed;* OR = 0.99, 95%CI 0.96 to 1.03, $p > 0.05$, $I^2 = 55\%$, $Qp < 0.05$ For males only: OR = 0.95, 95%CI 0.87 to 1.04, $p > 0.05$, $I^2 = 57\%$, $Qp < 0.05$ For females only: OR = 0.96, 95%CI 0.85 to 1.09, $p > 0.05$, I^2 not reported, $Qp > 0.05$	
No significant differences in the number of cases of schizophrenia between people potentially exposed to influenza prenatally during any trimester and those potentially not exposed; First trimester: OR = 0.91, 95%CI 0.85 to 0.98, $p > 0.05$, $Qp > 0.05$ For males only: OR = 0.88, 95%CI 0.75 to 1.04, $p > 0.05$, $Qp > 0.05$ For females only: OR = 0.80, 95%CI 0.63 to 1.00, $p > 0.05$, $Qp > 0.05$ Second trimester: OR = 1.00, 95%CI 0.93 to 1.07, $p > 0.05$, $Qp > 0.05$ For males only: OR = 0.99, 95%CI 0.85 to 1.16, $p > 0.05$, $Qp < 0.05$ For females only: OR = 1.07, 95%CI 0.87 to 1.30, $p > 0.05$, $Qp > 0.05$ Third trimester: OR = 1.05, 95%CI 0.98 to 1.12, $p > 0.05$, $Qp < 0.05$ For males only: OR = 0.99, 95%CI 0.84 to 1.16, $p > 0.05$, $Qp > 0.05$ For females only: OR = 1.04, 95%CI 0.85 to 1.28, $p > 0.05$, $Qp > 0.05$	
Studies conducted in Japan where 1957 pandemic came in two waves and where approximately 50% of the population reported having had influenza	
No significant differences in the number of cases of schizophrenia between people in Japan potentially exposed to influenza prenatally and people in Japan potentially not exposed; 3 studies, N = unclear, RR = 0.98 (CI not reported) For Japanese men: RR = 0.92, 95%CI 0.81 to 1.04, $p > 0.05$, Qp not reported For Japanese women: RR = 1.08, 95%CI 0.92 to 1.26, $p > 0.05$, Qp not reported	
Consistency in results	Some inconsistency
Precision in results	Precise
Directness of results	Indirect measure of exposure
Comparison 2	**Studies examining the risk of schizophrenia among people born to mothers who were pregnant during the pandemic and reported having had influenza compared to mothers who were pregnant during the pandemic and reported not having had influenza.**

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Summary of evidence	**Moderate to low quality evidence (large sample, unable to assess consistency, imprecise, indirect) suggests no association between exposure to the 1957 influenza pandemic during pregnancy and risk of schizophrenia in the offspring.**
Exposure to influenza in utero	
No differences between groups; 2 studies, N = 16,529, RR = 1.20, 95%CI 0.59 to 2.42, $p > 0.05$, Qp not reported	
Consistency in results	Unable to assess; no measure of consistency is reported.
Precision in results	Imprecise
Directness of results	Indirect – exposure inferred through maternal infection

Zhang J, Luo W, Huang P, Peng L, Huang Q

Maternal C-reactive protein and cytokine levels during pregnancy and the risk of selected neuropsychiatric disorders in offspring: A systematic review and meta-analysis

Journal of Psychiatric Research 2018; 105: 86-94

View review abstract online

Comparison	**Maternal c-reactive protein and cytokine levels during pregnancy and risk of schizophrenia in the offspring.**
Summary of evidence	**High quality evidence (large sample, consistent, precise, direct) suggests a small effect of increased risk of schizophrenia in the offspring of women with increased c-reactive protein levels during pregnancy.** **Moderate to high quality evidence (imprecise) suggests small effects of increased risk of schizophrenia in the offspring of women with increased IL-8 or IL-10 during pregnancy.**
Serum c-reactive protein	
A significant, small effect of increased risk of schizophrenia in the offspring of women with increased c-reactive protein levels during pregnancy; 2 studies, N = 1,664, OR = 1.31, 95%CI 1.11 to 1.55, $p < 0.01$, $I^2 = 0\%$, $p = 0.97$	
Serum cytokines	

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Maternal illness during pregnancy

significant, small effects of increased risk of schizophrenia in the offspring of women with increased IL-8 or IL-10 during pregnancy; Pro-inflammatory cytokine IL-8: 5 studies, N = 496, OR = 1.64, 95%CI 1.06 to 2.55, $p = 0.03$, $I^2 = 33\%$, $p = 0.19$ Anti-inflammatory cytokine IL-10: 2 studies, N = 230, OR = 2.16, 95%CI 1.30 to 3.59, $p < 0.01$, $I^2 = 0\%$, $p = 0.98$ There were no associations with IL-1β, IL-2, IL-6 or TNF-α.	
Consistency in results	Consistent
Precision in results	Precise for c-reactive protein, imprecise for cytokines.
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), IL = interleukin, N = number of participants, OR = odds ratio, p = probability of obtaining that result ($p < 0.05$ generally regarded as significant), Q = measure of consistency, RR = risk ratio, TNF = tumor necrosis factor, vs. = versus

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.

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, an 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. An 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[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.

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) which 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[7].

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 dependent 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

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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).

‡ 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[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 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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