TECHNICAL COMMENTARY

NeuRA
Discover. Conquer. Cure.
SCHIZOPHRENIA LIBRARY

Obstetric complications

Introduction

Obstetric complications are a broad class of deviations from a normal course of events experienced during pregnancy, labour, delivery, and the early neonatal period. Studies have attempted to investigate whether any deviation or combination of deviations are related to the subsequent development of schizophrenia. Teasing out possible effects of obstetric complications is not simple because many other, and often unknown, contributing factors are most probably involved. Also see the maternal illness during pregnancy table.

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 five systematic reviews that met our inclusion criteria[3-7].

- Moderate quality evidence found medium-sized increased risk of psychotic disorders in general (mostly schizophrenia spectrum or non-affective psychosis) following exposure to congenital malformation or polyhydramnios. There were small effects of maternal hypertension, pre-eclampsia or toxaemia, hypoxia, ruptured membranes, blood loss in pregnancy (but not during labour), rhesus-associated factors and incompatibility, asphyxic state, low birth weight (<3000g), gestational age <37 weeks, and birth length <49cm. No associations were found for placental complications, caesarean section, prolonged labour, induced labour, instrument delivery, abnormal presentation, cephalopelvic disproportion, baby being kept in hospital or special care, need for incubator, non-spontaneous delivery, uterine atony, 5min apgar score <7, umbilical cord complications, abnormal fetal heart rate/ rhythm, or ponderal index.
- Compared to people with bipolar disorder, moderate quality evidence finds a medium-sized increased risk of ultra high-risk mental states and a small effect of increased risk of schizophrenia following exposure to any obstetric complication.

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

Obstetric complications

Dachew BA, Mamun A, Maravilla JC, Alati R

Association between hypertensive disorders of pregnancy and the development of offspring mental and behavioural problems: A systematic review and meta-analysis

Psychiatry Research 2018; 260: 458-67

View review abstract online

Comparison	**Exposure to pre-eclampsia in utero and schizophrenia in adulthood.**
Summary of evidence	**Moderate quality evidence (large sample, inconsistent, imprecise, direct) suggests a small effect of increased risk of schizophrenia in offspring exposed to preeclampsia in utero.**
Pre-eclampsia	
Small, significant increased risk of schizophrenia in offspring exposed to pre-eclampsia; 11 studies, N = 1,462,823, RR = 1.37, 95%CI, 1.08 to 1.72, I^2 = 64%, p < 0.001 Subgroup analyses revealed the effect size was larger in cohort vs. case-control studies, studies with large vs. small samples, and in good vs. poor quality studies.	
Consistency in results	Inconsistent
Precision in results	Imprecise
Directness of results	Direct

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**

Obstetric complications

	non-affective psychosis) in adulthood in people who were exposed to obstetric complications vs. controls.
Summary of evidence	**Moderate quality evidence (unclear sample size, some inconsistency and imprecision, direct) suggests medium-sized increased risk of psychotic disorders following exposure to congenital malformation or polyhydramnios. There were small effects of maternal hypertension, pre-eclampsia or toxaemia, hypoxia, ruptured membranes, blood loss in pregnancy (but not during labour), rhesus-associated factors and incompatibility, asphyxic state, low birth weight (<3000g), gestational age <37 weeks, and birth length <49cm.** **No associations were found for placental complications, caesarean section, prolonged labour, induced labour, instrument delivery, abnormal presentation, cephalopelvic disproportion, baby being kept in hospital or special care, non-spontaneous delivery, uterine atony, 5min apgar score <7, umbilical cord complications, abnormal fetal heart rate/ rhythm, ponderal index, or need for incubator.**
All obstetric complications	
A small, significant increased risk of psychotic disorders following exposure to any obstetric complication; Unspecified: 19 studies, N not reported, OR = 1.52, 95%CI 1.19 to 1.94, $p = 0.0007$, $I^2 = 67\%$, $p < 0.0001$ Definite: 9 studies, N not reported, OR = 1.83, 95%CI 1.21 to 2.77, $p = 0.0042$, $I^2 = 71\%$, $p = 0.0005$	
Polyhydramnios	
A medium-sized, significant effect of increased risk of psychotic disorders following exposure to polyhydramnios; 3 studies, N not reported, OR = 3.05, 95%CI 1.15 to 8.06, $p = 0.025$, $I^2 = 0\%$, $p = 1.00$	
Congenital malformation	
A medium-sized, significant effect of increased risk of psychotic disorders following exposure to congenital malformation; 4 studies, N not reported, OR = 2.35, 95%CI 1.23 to 4.46, $p = 0.0093$, $I^2 = 0\%$, $p = 0.82$	
Asphyxic state	
A small significant effect of increased risk of psychotic disorders following exposure to asphyxic state;	

Obstetric complications

8 studies, N not reported, OR = 1.93, 95%CI 1.30 to 2.88, p = 0.0012, I^2 = 43%, p = 0.078
Maternal hypertension
A small, significant increased risk of psychotic disorders following exposure to maternal hypertension; 5 studies, N not reported, OR = 1.40, 95%CI 1.10 to 1.78, p = 0.0058, I^2 = 0%, p = 0.74
Hypoxia
A small, significant effect of increased risk of psychotic disorders following exposure to hypoxia; 6 studies, N not reported, OR = 1.63, 95%CI 1.11 to 2.40, p = 0.014, I^2 = 41%, p = 0.13
Ruptured membranes
A small, significant effect of increased risk of psychotic disorders following exposure to ruptured membranes; All: 5 studies, N not reported, OR = 1.86, 95%CI 1.23 to 2.83, p = 0.0033, I^2 = 0%, p = 0.77 After excluding studies using retrospective recall, this result was no longer significant. Premature: 4 studies, N not reported, OR = 2.29, 95%CI 1.38 to 3.80, p = 0.0013, I^2 = 0%, p = 0.80 *No significant effects of;* Preterm: 1 study, N not reported, OR = 1.20, 95%CI 0.58 to 2.51, p = 0.62
Blood loss during pregnancy
A small, significant effect of increased risk of psychotic disorders following exposure to blood loss in pregnancy; 11 studies, N not reported, OR = 1.54, 95%CI 1.06 to 2.25, p = 0.023, I^2 = 33%, p = 0.12
Gestational age
A small, significant effect of increased risk of psychotic disorders following exposure to gestational age <37 weeks; <37 weeks: 21 studies, N not reported, OR = 1.35, 95%CI 1.12 to 1.62, p = 0.0016, I^2 = 58%, p = 0.0002 *No significant effects of;* >42 weeks: 10 studies, N not reported, OR = 1.14, 95%CI 0.96 to 1.35, p = 0.13, I^2 = 25%, p = 0.19
Birth weight
Small, significant effects of increased risk of psychotic disorders following low birth weight;

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

Obstetric complications

<2000g: 13 studies, N not reported, OR = 1.84, 95%CI 1.53 to 2.22, $p < 0.0001$, $I^2 = 0\%$, $p = 0.83$
<2500g: 23 studies, N not reported, OR = 1.53, 95%CI 1.31 to 1.78, $p < 0.0001$, $I^2 = 25\%$, $p = 0.13$
2500−2999g: 15 studies, N not reported, OR = 1.23, 95%CI 1.15 to 1.31, $p < 0.0001$, $I^2 = 0\%$, $p = 0.92$
Small for gestational age: 10 studies, N not reported, OR = 1.40, 95%CI 1.25 to 1.57, $p < 0.0001$, $I^2 = 18\%$, $p = 0.26$
No significant effects of;
<2500g and premature: 4 studies, N not reported, OR = 1.53, 95%CI 0.90 to 2.60, $p = 0.12$, $I^2 = 13\%$, $p = 0.33$
3000−3499g: 15 studies, N not reported, OR = 1.00, 95%CI 0.95 to 1.05, $p = 0.92$, $I^2 = 0\%$, $p = 0.99$
Large or heavy for gestational age: 3 studies, N not reported, OR = 1.10, 95%CI 0.75 to 1.61, $p = 0.62$, $I^2 = 44\%$, $p = 0.17$
Small, significant effects of decreased risk of psychotic disorders following birth weight;
3500−3999g: 15 studies, N not reported, OR = 0.90, 95%CI 0.85 to 0.94, $p < 0.0001$, $I^2 = 0\%$, $p = 0.99$
>4000g: 15 studies, N not reported, OR = 0.86, 95%CI 0.80 to 0.92, $p < 0.0001$, $I^2 = 0\%$, $p = 0.76$
Rhesus-associated factors and incompatibility
A small, trend effect of increased risk of psychotic disorders following exposure to rhesus-associated factors and incompatibility;
9 studies, N not reported, OR = 1.42, 95%CI 1.00 to 2.01, $p = 0.051$, $I^2 = 0\%$, $p = 0.44$
Birth length
A small, trend effect of increased risk of psychotic disorders following exposure to birth length <49cm;
<49 cm: 8 studies, N not reported, OR = 1.17, 95%CI 1.05 to 1.32, $p = 0.057$, $I^2 = 21\%$, $p = 0.27$
No significant effects of;
>54 cm: 7 studies, N not reported, OR = 1.03, 95%CI 0.83 to 1.28, $p = 0.77$, $I^2 = 0\%$, $p = 0.79$
Head circumference
A small, trend effect of increased risk of psychotic disorders following exposure to head circumference <32cm;
<32cm: 10 studies, N not reported, OR = 1.37, 95%CI 0.99 to 1.91, $p = 0.057$, $I^2 = 14\%$, $p = 0.31$
Pre-eclampsia or toxaemia
A small, trend effect of increased risk of psychotic disorders following exposure to pre-eclampsia or

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

Obstetric complications

toxaemia; 14 studies, N not reported, OR = 1.32, 95%CI 0.99 to 1.76, p = 0.059, I^2 = 26%, p = 0.16
Placental complications
No significant effect of placental complications; 5 studies, N not reported, OR = 1.52, 95%CI 0.42 to 5.43, p = 0.52, I^2 = 60%, p = 0.040
Caesarean section
No significant effect of caesarean section; Any: 12 studies, N not reported, OR = 1.13, 95%CI 0.90 to 1.43, p = 0.30, I^2 = 42%, p = 0.052 Emergency: 9 studies, N not reported, OR = 1.41, 95%CI 0.87 to 2.30, p = 0.16, I^2 = 39%, p = 0.11
Prolonged labour
No significant effect of prolonged labour; 10 studies, N not reported, OR = 1.30, 95%CI 0.92 to 1.83, p = 0.14, I^2 = 47%, p = 0.037
Induced labour
No significant effect of induced labour; Oxytocics: 2 studies, N not reported, OR = 1.01, 95%CI 0.81 to 1.27, p = 0.91, I^2 = 0%, p = 0.58 Artificial rupture of membranes: 2 studies, N not reported, OR = 1.11, 95%CI 0.78 to 1.57, p = 0.57, I^2 = 61%, p = 0.053
Forceps, vacuum, instrumental delivery
No significant effect of instrument delivery; 14 studies, N not reported, OR = 1.15, 95%CI 0.91 to 1.46, p = 0.25, I^2 = 40%, p = 0.050
Abnormal presentation
No significant effect of abnormal presentation; Non-vertex: 10 studies, N not reported, OR = 1.03, 95%CI 0.77 to 1.39, p = 0.83, I^2 = 12%, p = 0.33 Breech: 5 studies, N not reported, OR = 1. 00, 95%CI 0.52 to 1.94, p = 0.99, I^2 = 0%, p = 0. 54
Cephalopelvic disproportion
No significant effect of cephalopelvic disproportion; 3 studies, N not reported, OR = 1.07, 95%CI 0.58 to 1.97, p = 0.83, I^2 = 21%, p = 0.28

Obstetric complications

Baby kept in hospital or special care
No significant effect of being kept in hospital or special care; 3 studies, N not reported, OR = 1.06, 95%CI 0.72 to 1.57, *p* = 0.76, I^2 = 62%, *p* = 0.031
Non-spontaneous delivery
No significant effect of non-spontaneous delivery; 3 studies, N not reported, OR = 0.98, 95%CI 0.78 to 1.24, *p* = 0.89, I^2 = 0%, *p* = 0.46
Uterine atony
No significant effect of uterine atony; 3 studies, N not reported, OR = 2.37, 95%CI 0.79 to 7.12, *p* = 0.12, I^2 = 39%, *p* = 0.20
Apgar score <7 at 5 min
No significant effect of apgar score <7; 5 studies, N not reported, OR = 1.57, 95%CI 0.94 to 2.63, *p* = 0.084, I^2 = 0%, *p* = 0.45
Umbilical cord complications
No significant effect of umbilical cord complications; Any: 7 studies, N not reported, OR = 1.13, 95%CI 0.93 to 1.39, *p* = 0.22, I^2 = 0%, *p* = 0.73 Umbilical cord around neck: 4 studies, N not reported, OR = 1.11, 95%CI 0.90 to 1.37, *p* = 0.32, I^2 = 0%, *p* = 0.66
Abnormal fetal heart rate or rhythm
No significant effect of abnormal fetal heart rate or rhythm; 3 studies, N not reported, OR = 1.17, 95%CI 0.80 to 1.73, *p* = 0.42, I^2 = 0%, *p* = 0.40
Maternal blood loss during delivery
No significant effect of maternal blood loss during delivery; 3 studies, N not reported, OR = 1.12, 95%CI 0.27 to 4.73, *p* = 0.88, I^2 = 61%, *p* = 0.075
Ponderal index
No significant effect of low or high ponderal index; Low index ≤5th centile: 2 studies, N not reported, OR = 1.17, 95%CI 0.82 to 1.67, *p* = 0.38, I^2 = 6%, *p* = 0.36

High index ≥95th centile: 2 studies, N not reported, OR = 1.13, 95%CI 0.80 to 1.60, p = 0.47, I^2 = 0%, p = 0.79
Need for incubator
No significant effect of need for incubator; 3 studies, N not reported, OR = 2.54, 95%CI 0.69 to 9.37, p = 0.16, I^2 = 0%, p = 0.43

Consistency in results	Some inconsistency
Precision in results	Some imprecision
Directness of results	Direct

Fusar-Poli P, Tantardini M, De Simone S, Ramella-Cravaro V, Oliver D, Kingdon J, Kotlicka-Antczak M, Valmaggia L, Lee J, Millan MJ, Galderisi S, Balottin U, Ricca V, McGuire P

Deconstructing vulnerability for psychosis: Meta-analysis of environmental risk factors for psychosis in subjects at ultra high-risk

European Psychiatry 2017; 40: 65-75

View review abstract online

Comparison	**Obstetric complications in people with ultra high-risk (UHR) mental states, which are determined as; attenuated psychotic symptoms, brief and limited intermittent psychotic symptoms, and genetic risk and functional deterioration.**
Summary of evidence	**Moderate quality evidence (small sample, consistent, imprecise, direct) suggests a medium-sized relationship between obstetric complications in general and ultra high-risk mental states.**

Obstetric complications
A significant medium-sized association between unspecified obstetric complications and the UHR state; 2 studies, N = 211, OR = 3.06, 95%CI 1.813 to 5.171, p < 0.001, I^2 = 0%, p = 0.585 There were no significant associations between UHR and caesarean delivery. There was no evidence of publication bias

Consistency in results	Consistent

Obstetric complications

Precision in results	Imprecise
Directness of results	Direct

Scott J, McNeill Y, Cavanagh J, Cannon M, Murray R

Exposure to obstetric complications and subsequent development of bipolar disorder: Systematic review

British Journal of Psychiatry 2006; 189: 3-11

View review abstract online

Comparison	**Obstetric complications and schizophrenia vs. bipolar disorder in adulthood.**
Summary of evidence	**Moderate quality evidence (large sample, imprecise, unable to assess consistency, direct) suggests a small increased risk of schizophrenia compared to bipolar disorder with exposure to obstetric complications in general.**

Obstetric complications

Small, significant effect of an increased risk of schizophrenia with exposure to obstetric complications;

5 studies, N = 640, OR = 0.61, 95%CI 0.39 to 0.95, *p* = 0.035, Q,*p* value not reported

Similar results were found in analyses of studies controlling possible confounders; sex, maternal age, or socioeconomic status and another assessing study quality.

Consistency in results	Unable to assess; no measure of consistency is reported.
Precision in results	Imprecise
Directness of results	Direct

Zhang T, Sidorchuk A, Sevilla-Cermeno L, Vilaplana-Perez A, Chang Z, Larsson H, Mataix-Cols D, Fernandez De La Cruz L

Association of Cesarean Delivery with Risk of Neurodevelopmental and Psychiatric Disorders in the Offspring: A Systematic Review and Meta-

Obstetric complications

analysis	
JAMA Network Open 2019; 2(8): e1910236 View review abstract online	
Comparison	**Association between caesarean delivery and the development of schizophrenia by 29 years.** **Note: the sample included people with schizophrenia and other non-affective psychoses.**
Summary of evidence	**Moderate to high quality evidence (large sample, inconsistent, precise, direct) finds no association between caesarean section and schizophrenia.**
Elective and emergency caesarean section	
No significant association; 5 studies, N >1.5M, OR = 0.97, 95%CI 0.78 to 1.21, $p > 0.05$, $I^2 = 83\%$ The results were similar in the subgroup analysis of elective and emergency caesarean.	
Consistency in results	Inconsistent
Precision in results	Precise
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), Q = Q statistic (chi-square) for the test of heterogeneity in results across studies, RR = risk ratio, vs. versus

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

NeuRA Discover. Conquer. Cure.

SCHIZOPHRENIA LIBRARY

Obstetric complications

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[8].

† 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[9]. 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) 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[8].

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).

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

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.

‡ 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[10].

‖ 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.

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

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. Scott J, McNeill Y, Cavanagh J, Cannon M, Murray R (2006): Exposure to obstetric complications and subsequent development of bipolar disorder: Systematic review. *British Journal of Psychiatry* 189: 3-11.
4. Fusar-Poli P, Tantardini M, De Simone S, Ramella-Cravaro V, Oliver D, Kingdon J*, et al.* (2017): Deconstructing vulnerability for psychosis: Meta-analysis of environmental risk factors for psychosis in subjects at ultra high-risk. *European Psychiatry* 40: 65-75.
5. Dachew BA, Mamun A, Maravilla JC, Alati R (2018): Association between hypertensive disorders of pregnancy and the development of offspring mental and behavioural problems: A systematic review and meta-analysis. *Psychiatry Research* 260: 458-67.
6. Zhang T, Sidorchuk A, Sevilla-Cermeno L, Vilaplana-Perez A, Chang Z, Larsson H*, et al.* (2019): Association of Cesarean Delivery with Risk of Neurodevelopmental and Psychiatric Disorders in the Offspring: A Systematic Review and Meta-analysis. *JAMA Network Open* 2 (8) (no pagination).
7. Davies C, Segre G, Estrade A, Radua J, De Micheli A, Provenzani U*, et al.* (2020): Prenatal and perinatal risk and protective factors for psychosis: a systematic review and meta-analysis. *The Lancet Psychiatry* 7: 399-410.
8. CochraneCollaboration (2008): Cochrane Handbook for Systematic Reviews of Interventions. Accessed 24/06/2011.
9. Rosenthal JA (1996): Qualitative Descriptors of Strength of Association and Effect Size. *Journal of Social Service Research* 21: 37-59.
10. GRADEpro (2008): [Computer program]. Jan Brozek, Andrew Oxman, Holger Schünemann. *Version 32 for Windows*

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