TECHNICAL COMMENTARY

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SCHIZOPHRENIA LIBRARY

Maternal diet and body mass

Introduction

Consumption of a balanced diet during pregnancy aids the development of a healthy fetus which may act as a preventative factor for the development of schizophrenia in adulthood. In contrast, consumption of substances or poor diet during pregnancy can be harmful to the developing fetus.

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 inclusion criteria[3-7].

- Moderate quality evidence suggests a small effect of increased risk of schizophrenia after exposure to famine or nutritional deficit in utero.
- Moderate quality evidence suggests medium-sized effects of increased risk of schizophrenia in offspring of mothers with low retinol during the 2nd trimester of pregnancy, high serum docosahexaenoic acid (an omega-3 fatty acid) during pregnancy at any stage, high pregnancy, or pre-pregnancy BMI, or in offspring with low neonatal vitamin D levels.
- Moderate to low quality evidence suggests greater fish consumption during pregnancy may lower the risk of schizophrenia in the offspring.

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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

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Comparison	**Risk of psychotic disorders (mostly schizophrenia spectrum or non-affective psychosis) in adulthood in people who were exposed to poor maternal diet in utero vs. controls.**
Summary of evidence	**Moderate quality evidence (unclear sample size, inconsistent, precise, direct) suggests a small increased risk of psychotic disorders (mostly schizophrenia spectrum or non-affective psychosis) following exposure to famine or nutritional deficit in utero.**
Maternal diet	
Small effects of increased risk of psychotic disorders following exposure in utero to; Any famine or nutritional deficit: 11 studies, N not reported, OR = 1.40, 95%CI 1.17 to 1.68, p = 0.0001, I^2 = 69% Famine: 3 studies, N not reported, OR = 1.61, 95%CI 1.51 to 1.71, p <0.0001, I^2 = 0% There were no associations with maternal anaemia or maternal haemoglobin.	
Consistency in results‡	Inconsistent for overall analysis, consistent for famine
Precision in results§	Precise
Directness of results‖	Direct

Khandaker GM, Dibben CRM, Jones PB

Does maternal body mass index during pregnancy influence risk of

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schizophrenia in the adult offspring

Obesity Reviews 2012; 13(6): 518-527

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Comparison	**High body mass index during or pre-pregnancy vs. low or normal range body mass index during pregnancy and the risk of schizophrenia in their offspring.**
Summary of evidence	**Moderate quality evidence (mostly large samples, direct, some imprecision, unable to assess consistency) suggests a medium-sized effect of increased risk of schizophrenia in offspring of mothers with high pre-pregnancy and pregnancy BMI.**

Body mass index

1 Japanese study (N = 336) reported a significant, small effect of increased risk of schizophrenia in offspring of mothers who had high BMI during pregnancy;

Early pregnancy: OR = 1.24, 95%CI 1.02 to 1.50, $p < 0.05$

Late pregnancy: OR = 1.19, 95%CI 1.01 to 1.41, $p < 0.05$

These results are adjusted for birth order and gestational age of offspring.

However, 1 Finnish study (N = 7,200) reported a significant, medium-sized effect of increased risk of schizophrenia in offspring of mothers who had low BMI during late pregnancy;

BMI < 24 vs. BMI > 30: OR = 3.75, 95%CI 1.42 to 9.89, $p < 0.05$

Review authors suggest that this finding could be confounded by poverty factors.

1 USA study (N = 6,633) reported a significant, medium-sized effect of increased risk of schizophrenia in offspring of mothers who had high pre-pregnancy BMI;

BMI > 30 vs. BMI 20 to 26.9: OR = 2.9, 95%CI 1.3 to 6.6, $p < 0.05$

These results are adjusted for maternal age, ethnicity, parity, smoking and education.

Another Finnish study (N = 10,578) reported a trend effect of increased risk of schizophrenia in offspring of mothers who had high pre-pregnancy BMI;

BMI > 30 vs. BMI 19: OR = 2.1, 95%CI 0.9 to 4.6, $p = 0.07$

These results are adjusted for gender of offspring, social class, and maternal age at conception.

Consistency in results	No measures of heterogeneity reported, appears inconsistent
Precision in results	Mostly imprecise
Directness of results	Direct

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Kinney DK, Teixeira P, Hsu D, Napoleon SC, Crowley DJ, Miller A, Hyman W, Huang E

Relation of Schizophrenia Prevalence to Latitude, Climate, Fish Consumption, Infant Mortality, and Skin Color: A Role for Prenatal Vitamin D Deficiency and Infections?

Schizophrenia Bulletin 2009; 35(3): 582-595

View review abstract online

Comparison	**Estimated maternal fish consumption during pregnancy and relationship to regional prevalence of schizophrenia, controlling for latitude.** **Fish consumptions (kg/person/year) is estimated from regional fish consumption levels 25 years prior to when study was conducted, as authors state that the average age of onset for schizophrenia is early to middle 20's.**
Summary of evidence	**Moderate to low quality evidence (large samples, indirect, unable to assess precision and consistency) suggests a relationship between higher fish consumption during pregnancy and lower risk of developing schizophrenia in the offspring.**
Maternal fish consumption and regional prevalence of schizophrenia	
Significant relationship between higher estimated maternal fish consumption and lower regional prevalence of schizophrenia; 48 prevalence studies N = 2,392,325, GLM main effects for fish consumption; $F_{1,47} = 4.56$, $p = 0.038$	
Subgroup analysis including only Scandinavian countries as high latitude/cool climate countries show greater prevalence of schizophrenia generally; 9 prevalence studies, N = 359,263, GLM main effects for fish consumption; $F_{1,8} = 107.0$, $p = 0.0001$ There was an interaction between latitude within the Scandinavian region and fish consumption, with risk for schizophrenia increasing as latitude increases and fish consumption decreases; $F_{1,8} = 11.8$, $p = 0.02$.	
Consistency in results	Unable to assess; no measures of heterogeneity is reported.
Precision in results	Unable to assess; no confidence intervals are reported.

Directness of results	Indirect – individual maternal fish consumption estimated from regional consumption

Li C, Lumey LH

Exposure to the Chinese famine of 1959-61 in early life and long-term health conditions: a systematic review and meta-analysis

International Journal of Epidemiology 2017; 46: 1157-70

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Comparison	**Exposure to famine in utero and/or childhood and later risk of schizophrenia.**
Summary of evidence	**Moderate quality evidence (large sample, precise, inconsistent, indirect) suggests a small effect of increased risk of schizophrenia after exposure to famine in utero and/or childhood.**
Famine	
A small, significant increased risk of schizophrenia with exposure to famine; 2 regional studies, N = 900,353, OR = 1.52, 95%CI 1.29 to 1.77, $p < 0.05$, $I^2 = 81.2\%$ Authors report that both studies were high quality.	
Consistency in results	Inconsistent
Precision in results	Precise
Directness of results	Indirect measure of exposure

Laurens KR, Luo L, Matheson SL, Carr VJ, Raudino A, Harris F, Green MJ

Common or distinct pathways to psychosis? A systematic review of evidence from prospective studies for developmental risk factors and antecedents of the schizophrenia spectrum disorders and affective psychoses

BMC Psychiatry 2015; 15: 205.DOI 10.1186/s12888-015-0562-2

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Comparison	Diet, substance use and BMI during pregnancy.
Summary of evidence	**Moderate quality evidence (medium to large samples, direct, imprecise, unable to assess consistency) suggests medium-sized effects of increased risk of schizophrenia in offspring of mothers with low retinol during the 2nd trimester of pregnancy, high serum docosahexaenoic acid (an omega-3 fatty acid) during pregnancy, high pre-pregnancy BMI, or in offspring with low neonatal vitamin D levels, No effects were reported for maternal smoking during pregnancy.**
Maternal dietary factors	
1 study (N = 156) reported a significant, medium-sized effect of increased risk of schizophrenia in the offspring of mothers with low retinol during the 2nd trimester of pregnancy, but no differences were found in retinol levels during the 3rd trimester; 2nd trimester: OR = 3.06, 95%CI 1.06 to 8.79, $p < 0.05$ 3rd trimester: OR = 1.59, 95%CI 0.47 to 5.38, $p > 0.05$ This study controlled for maternal age, and maternal education, and controls were matched on age, sex, gestational timing of first maternal serum sample, and number of maternal blood samples drawn during pregnancy.	
1 study (N = 152) reported a significant, medium-sized effect of increased risk of schizophrenia in the offspring of mothers with high serum docosahexaenoic acid (an omega-3 fatty acid) during pregnancy high pre-pregnancy BMI; OR = 2.51, 95%CI 1.28 to 4.93, $p < 0.05$	
1 study (N = 860) reported a significant, small to medium-sized effect of increased risk of adult schizophrenia in offspring with low vitamin D levels in the neonatal period; First quintile vs. fourth: RR = 2.1, 95%CI 1.3 to 3.5, $p < 0.05$ Second quintile vs. fourth: RR = 2.0, 95%CI 1.3 to 3.2, $p < 0.05$ Third quintile vs. fourth: RR = 2.1, 95%CI 1.3 to 3.4, $p < 0.05$ Fifth quintile vs. fourth: RR = 1.71, 95%CI 1.04 to 2.8, $p < 0.05$	
1 study (N = 8,823) reported a significant, medium-sized effect of reduced risk of schizophrenia in adulthood with vitamin D dosage ≥2000 IU/day given during the first year of life for male offspring; Males: RR = 0.23, 95%CI 0.06 to 0.95, $p < 0.05$ Females: RR = 0.99, 95%CI 0.14 to 7.19, $p > 0.05$ This study controlled for parity, gestational and maternal age, length of maternal education, SES, birth weight.	
3 studies reported small to medium-sized associations between high pre-pregnancy BMI and schizophrenia in the offspring;	

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N = 6,633, high maternal pre-pregnant BMI (≥30kg/m2): OR = 3.00, 95%CI 1.35 to 6.64, $p < 0.05$ N = 7,780, low maternal BMI (<19.9 kg/m^2): OR = 1.00, 95%CI 0.57 to 1.75, $p > 0.05$, average maternal BMI (20-26.9 kg/m^2): OR = 0.71, 95%CI 0.44 to 1.14, $p > 0.05$, above average maternal BMI (27-29.9 kg/m^2): OR = 1.36, 95%CI 0.57 to 3.25, $p > 0.05$, high maternal BMI (>30kg/m^2): OR = 3.59, 95%CI 1.63 to 7.93, $p < 0.01$ N = 336, high BMI first antenatal visit OR = 1.24, 95%CI 1.02 to 1.50, $p < 0.05$, high BMI last antenatal visit: OR = 1.19, 95%CI 1.00 to 1.41, $p < 0.05$ The latter study controlled for age, birth order, and gestational age at first or last antenatal care visit. *2 studies reported no increased risk of schizophrenia in adulthood with maternal smoking during pregnancy;* N = 164, any maternal smoking: OR = 0.92, 95%CI 0.48 to 1.75, $p > 0.05$ N = 1144, maternal smoking in 2nd trimester: OR = 1.10, 95%CI 0.50 to 2.10, $p > 0.05$ The latter study controlled for sex, SES, status at birth, maternal depression.	
Consistency in results	Unable to assess, no heterogeneity measure is reported.
Precision in results	Imprecise
Directness of results	Direct

Explanation of acronyms

CI = confidence interval, GLM *F* = general linear model F for testing differences between groups, 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), RR = risk ratio, SES = socio-economic status

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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[8].

† Different effect measures are reported by different reviews.

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[8].

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.

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

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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).

‡ 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.

‖ 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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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. Li C, Lumey LH (2017): Exposure to the Chinese famine of 1959-61 in early life and long-term health conditions: a systematic review and meta-analysis. *International Journal of Epidemiology* 46: 1157-70.
4. Laurens K, Luo L, Matheson S, Carr V, Raudino A, Harris F, *et al.* (2015): Common or distinct pathways to psychosis? A systematic review of evidence from prospective studies for developmental risk factors and antecedents of the schizophrenia spectrum disorders and affective psychoses. *BMC Psychiatry* 15: 205.
5. Kinney DK, Teixeira P, Hsu D, Napoleon SC, Crowley DJ, Miller A, *et al.* (2009): Relation of Schizophrenia Prevalence to Latitude, Climate, Fish Consumption, Infant Mortality, and Skin Color: A Role for Prenatal Vitamin D Deficiency and Infections? *Schizophrenia Bulletin* 35: 582-95.
6. Khandaker GM, Dibben CR, Jones PB (2012): Does maternal body mass index during pregnancy influence risk of schizophrenia in the adult offspring? *Obesity Reviews* 13: 518-27.
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.