TECHNICAL COMMENTARY

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SCHIZOPHRENIA LIBRARY

Sibship

Introduction

Sibship is a medical term meaning a group of individuals born of the same parents. Factors associated with sibship include birth order, number of siblings or number of births in the family, and inter-birth interval periods. It is not known how these factors may be associated with 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 two systematic reviews that met our inclusion criteria[3, 4].

- Moderate quality evidence suggests a small to medium-sized increased risk of schizophrenia in people who had one, four or five births in their family, or in children born less than 18 months before or after their closest sibling. First birth order may be associated with a reduced risk of schizophrenia.

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

Harper S, Towers-Evans H, MacCabe J

The aetiology of schizophrenia: what have the Swedish Medical Registers taught us?

Social Psychiatry and Psychiatric Epidemiology 2015; 50: 1471-1479

View review abstract online

Comparison	**Number of births in the family and inter-birth interval in Swedish populations with schizophrenia vs. Swedish population without schizophrenia.**
Summary of evidence	**Moderate quality evidence (large samples, imprecise, unable to assess consistency, direct) suggests small to medium-sized increased risk of schizophrenia in adulthood in children who had four or more births in their family, or in children born less than 12 months after their closest sibling.**

Number of births in the family

One study (N = 1,002) reported a significant, medium-sized effect of greater odds of schizophrenia in people who had four or more births in their family compared to people who had fewer than four births in their family:

OR = 2.00, 95%CI 1.30 to 2.80, $p < 0.05$

Inter-birth interval

One study (N = 183,921) reported significant, small to medium-sized effects of greater odds of schizophrenia in people who were born within six to 12 months after their closest sibling:

6 month vs. 13 to 24 month retrograde birth interval: OR = 3.29, 95%CI 2.00 to 5.41, $p < 0.05$

7 to 12 month vs. 13 to 24 month retrograde birth interval: OR = 1.96, 95%CI 1.27 to 3.05, $p < 0.05$

These effects were reduced slightly, but remained significant, after adjusting for age, larger families, younger parents, lower income, socioeconomic position, and family history of psychosis.

No association was found for those born six months before their closest sibling:

6 months vs. 13 to 24 months anterograde birth interval: OR = 0.73, 95%CI 0.38 to 1.40, $p = 0.28$

Consistency in results‡	Unable to assess; one study per outcome.
Precision in results§	Imprecise
Directness of results‖	Direct

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

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(1): 205

View review abstract online

Comparison	**Sibship factors in people with schizophrenia vs. controls.**
Summary of evidence	**Moderate quality evidence (large samples, mostly imprecise, appears inconsistent, direct) suggests a small to medium-sized increased risk of schizophrenia in people who had one, four or five births in their family, or in children born less than 18 months before or after their closest sibling. First birth order may be associated with a reduced risk of schizophrenia.**

Number of births in the family

One study reported a significant, small to medium-sized increased odds of schizophrenia in people who had one birth in their family compared to more births, however another study reported no significant differences when comparing one birth with two to three births:

1 vs. all other: N = 1,301,522, OR = 1.98, 95%CI 1.58 to 2.47, $p < 0.01$

1 vs. 2 to 3: N = 1,002, OR = 1.30, 95%CI 0.60 to 1.90, $p > 0.05$

One study reported a significant, small increased odds of schizophrenia in people who had four or five births in their family compared to two births:

2 vs. 3: N = 21,059, OR = 1.13, 95%CI 0.94 to 1.35, $p > 0.05$

2 vs. 4: N = 21,059, OR = 1.28, 95%CI 1.04 to 1.58, $p < 0.05$

2 vs. 5: N = 21,059, OR = 1.29, 95%CI 1.02 to 1.62, $p < 0.05$

All of these results were adjusted for sex, ages of other siblings, birth order, birth cohort, maternal age, paternal age, sex of youngest proband, lowest age-at-onset in the sibship, and maternal schizophrenia.

One study reported a significant, medium-sized increased odds of schizophrenia in people whose mother had more than two previous pregnancies compared with any other number of pregnancies:

>2 previous babies vs. all other: N = 16,847, OR = 2.41, 95%CI 1.18 to 4.89, $p < 0.05$

Two studies reported a small to medium-sized increased odds of schizophrenia in people with four or more births in their family:

≥4 births vs. all other number of births: N = 1,301,522, OR = 1.31, 95%CI 1.09 to 1.57, $p < 0.01$

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

≥4 births vs. 2 to 3 births: N = 1,002, OR = 2.00, 95%CI 1.30 to 2.80, $p < 0.05$

The latter study adjusted for maternal age at delivery, parity, hypertensive disease, diabetes, bleeding during pregnancy, uterine atony, birth weight for gestational age, ponderal index, apgar score at one minute, asphyxia, late winter birth, and controls matched on sex, year of birth, and hospital of birth.

One study reported a significant, small decreased odds of schizophrenia in people who had two to three births in their family compared to any other number of births:

2-3 vs. all other: N = 1,301,522, OR = 0.61, 95%CI 0.52 to 0.71, $p < 0.01$

One study reported no significant differences when comparing 6 or more births with five or fewer births:

≥6 vs. ≤ 5: N = 10,719, OR = 1.38, 95%CI 0.78 to 2.45, $p > 0.05$

Number of miscarriages or abortions

One study reported no significant differences for the number of maternal miscarriages or abortions and risk of schizophrenia:

Maternal miscarriages: N = 237, OR = 0.54, 95%CI 0.20 to 1.48, $p > 0.05$

Maternal abortions: N = 237, OR = 1.03, 95%CI 0.12 to 8.56, $p > 0.05$

Twin birth

One study reported a significant, medium-sized decreased odds of schizophrenia in families with twins, while another study reported no significant differences:

N = 1,546, OR = 0.31, 95%CI 0.21 to 0.72, $p < 0.01$

N = 1,002, OR = 2.60, 95%CI 0.64 to 10.56, $p > 0.05$

Birth order

One study reported a significant, small to medium-sized decreased odds of schizophrenia in first-born children compared to any other birth order:

First vs. second: N = 21,059, OR = 0.62, 95%CI 0.54 to 0.72, $p < 0.05$

First vs. third: N = 21,059, OR = 0.54, 95%CI 0.44 to 0.67, $p < 0.05$

First vs. fourth or higher: N = 21,059, OR = 0.50, 95%CI 0.38 to 0.67, $p < 0.05$

All of these results were adjusted for sex, ages of other siblings, birth order, birth cohort, maternal age, paternal age, sex of youngest proband, lowest age-at-onset in the sibship, and maternal schizophrenia.

A much smaller study reported a significant, medium-sized increased odds of schizophrenia in first-born children, and decreased odds for children born in other birth orders:

First birth order: N = 336, OR = 2.48, 95%CI 1.36 to 4.52, $p < 0.01$

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

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Other birth order: N = 336, OR = 0.40, 95%CI 0.22 to 0.73, $p < 0.01$ *One study reported a significant, small increased odds of schizophrenia for children with short retrograde or anterograde birth intervals (< 18 months):* <18-month retrograde birth interval: N = 897,685, OR = 1.21, 95%CI 1.04 to 1.40, $p < 0.05$ <18-month anterograde birth interval: N = 897,685, OR = 1.54, 95%CI 1.33 to 1.77, $p < 0.01$	
Consistency in results	Appears inconsistent.
Precision in results	Mostly imprecise
Directness of results	Direct

Explanation of acronyms

CI = confidence interval, N = number of participants, OR = odds ratio, *p* = statistical probability of obtaining that result ($p < 0.05$ generally regarded as significant), Q = Q statistic for the test of heterogeneity, vs. = versus

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

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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[5].

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† 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. Standardized 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 moderate effect, and 0.8 and over represents a large effect[5].

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[6]. 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 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[5];

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

§ 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[7].

‖ 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.

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

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