TECHNICAL COMMENTARY

Parental age

Introduction

There have been claims that advanced parental age may be a risk factor for the development of mental disorders in the offspring. Commonly offered explanations have been the occurrence of germline mutations in older adults and/or psychological factors such as earlier than normal parental death experienced at a vulnerable age. Pinpointing the age at which parenthood may be associated with a significantly higher risk of bipolar disorder could be useful knowledge for potential parents, particularly if there is a pre-existing increased genetic risk of developing the disorder.

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 2010 that report results separately for people with a diagnosis of bipolar or related disorders. 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, and PsycINFO. Hand searching reference lists of identified reviews was also conducted. When multiple copies of reviews assessing the same topic were found, only the most recent version and/or comprehensive review 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 two systematic reviews that met our inclusion criteria[3, 4].

- High quality evidence finds a small increase in the odds of bipolar disorder in people whose father was aged over 40 years at their birth.
- Moderate to low quality evidence finds a significant, medium-sized increase in the odds of affective psychosis (including bipolar disorder) in people whose mother was over 34 years at their birth.

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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	**Risk of developing bipolar disorder with older parental age at birth.**
Summary of evidence	**Moderate to low quality evidence (mostly imprecise, one study, direct, large samples) suggests a significant, medium-sized effect of increased odds of affective psychosis (including bipolar disorder) in people whose mother was 34 years or older at their birth compared to having a mother who was younger than 34 years at their birth.** **There were significant, small effects of increased odds of bipolar disorder in people whose father was aged between 31-44 years or 51-55 years at their birth compared to fathers aged 21-25 years. There were no differences in one study for any paternal age group using 25-29 years as the comparison group.**

Maternal age at birth

A significant, medium-sized effect of increased odds of affective psychosis (including bipolar disorder) in people whose mother was 34 or older at their birth:

≥34 years: 1 study, N = 16,844, OR = 2.29, 95%CI 1.03 to 5.11, $p < 0.05$

However, two other studies found no associations between maternal age and risk of affective psychosis;

<17 years: 1 study, N = 1,301,522, OR = 0.76, 95%CI 0.05 to 12.25, $p > 0.05$

<19 years: 1 study, N = 1,301,522, OR = 1.00, 95%CI 0.55 to 1.83, $p > 0.05$

≤19 years: 1 study, N = 1,188, OR = 1.00, 95%CI 0.50 to 2.00, $p > 0.05$

≥30 years: 1 study, N = 1,188, OR = 1.40, 95%CI 0.90 to 2.00, $p > 0.05$

>30 years: 1 study, N = 1,301,522, OR = 1.25, 95%CI 0.95 to 1.65, $p > 0.05$

≥40 years: 1 study, N = 1,301,522, OR = 0.83, 95%CI 0.22 to 3.17, $p > 0.05$

Paternal age at birth

Significant, small effects of increased odds of bipolar disorder in people whose father was aged

between 31-44 years or 51-55 years at their birth (compared to 21-25 years): 31-35 years: 1 study, N = 49,538, RR = 1.21, 95%CI 1.09 to 1.34, $p < 0.05$ 35-39 years: 1 study, N = 711,989, HR = 1.68, 95%CI 1.09 to 2.61, $p < 0.05$ 36-40 years: 1 study, N = 49,538, RR = 1.25, 95%CI 1.09 to 1.42, $p < 0.05$ 40-44 years: 1 study, N = 711,989, HR = 1.85, 95%CI 1.04 to 3.30, $p < 0.05$ 51-55 years: 1 study, N = 49,538, RR = 1.71, 95%CI 1.21 to 2.41, $p < 0.05$ *There were no associations found between fathers aged 21-25 years and;* ≤20 years: 1 study, N = 49,538, OR = 0.89, 95%CI 0.75 to 1.07, $p > 0.05$ <21 years: 1 study, N = 711,989, HR = 1.35, 95%CI 0.67 to 2.75, $p > 0.05$ 25-29 years: 1 study, N = 711,989, HR = 1.15, 95%CI 0.83 to 1.59, $p > 0.05$ 26-30 years: 1 study, N = 49,538, OR = 1.08, 95%CI 0.98 to 1.18, $p > 0.05$ 30-34 years: 1 study, N = 711,989, HR = 1.41, 95%CI 0.99 to 2.00, $p > 0.05$ 41-45 years: 1 study, N = 49,538, OR = 1.14, 95%CI 0.96 to 1.36, $p > 0.05$ 45-49 years: 1 study, N = 711,989, HR = 1.06, 95%CI 0.39 to 2.83, $p > 0.05$ 46-50 years: 1 study, N = 49,538, OR = 1.26, 95%CI 0.99 to 1.61, $p > 0.05$ ≥50 years: 1 study, N = 711,989, HR = 1.43, 95%CI 0.43 to 4.76, $p > 0.05$ ≥56 years: 1 study, N = 49,538, OR = 1.03, 95%CI 0.53 to 2.01, $p > 0.05$ *There were no associations found between fathers aged 25-29 years and;* <20 years: 1 study, N = 5,605, OR = 1.68, 95%CI 0.94 to 3.01, $p > 0.05$ 20-24 years: 1 study, N = 5,605, OR = 0.82, 95%CI 0.65 to 1.03, $p > 0.05$ 30-34 years: 1 study, N = 5,605, OR = 1.12, 95%CI 0.96 to 1.32, $p > 0.05$ 35-39 years: 1 study, N = 5,605, OR = 0.99, 95%CI 0.80 to 1.22, $p > 0.05$ ≥40 years: 1 study, N = 5,605, OR = 1.14, 95%CI 0.84 to 1.55, $p > 0.05$	
Consistency in results‡	N/A; one study
Precision in results§	Mostly imprecise
Directness of results‖	Direct

Rodriguez V, Alameda L, Trotta G, Spinazzola E, Marino P, Matheson SL, Laurens KR, Murray RM, Vassos E

Environmental Risk Factors in Bipolar Disorder and Psychotic Depression: A Systematic Review and Meta-Analysis of Prospective Studies

Parental age

Schizophrenia Bulletin 2021; https://doi.org/10.1093/schbul/sbaa197 View review abstract online	
Comparison	**Risk of bipolar disorder with paternal age >40 years at birth compared to <40 years.**
Summary of evidence	**High quality evidence (large sample, consistent, precise, direct) finds a small increased odds of bipolar disorder in people whose father was over 40 years at their birth.**
Paternal age at birth	
Significant, small effect of increased odds of bipolar disorder in people whose father was aged >40 years at their birth: 5 studies, N = 23,813, OR = 1.17, 95%CI 1.11 to 1.22, $p < 0.05$, $I^2 = 0\%$	
Consistency in results	Consistent
Precision in results	Precise
Directness of results	Direct

Explanation of acronyms

CI = confidence interval, HR = hazard ratio, 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, 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.

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† Different effect measures are reported by different reviews.

Median rate ratio refers to the ratio between prevalence or incidence rates of two groups, based on the median rather than the mean. The median is often used as a better measure of central tendency than the mean when data are skewed. Harmonic means are also used when data are skewed and are appropriate for rate data.

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[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, 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[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 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

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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).

‡ 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[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 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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