TECHNICAL COMMENTARY

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Parental age

Introduction

There have been claims that advanced parental age may be a risk factor for the development of schizophrenia 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 schizophrenia 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 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 six reviews that met our inclusion criteria[3-8].

- Moderate to high quality evidence suggests an increased risk of schizophrenia in adulthood when paternal age was over 35 years at birth, with risk greatest with paternal age over 54 years. Moderate quality evidence suggests an increased risk when paternal age was less than 20 to 25 years.
- Moderate quality evidence finds small, significant effects of increased risk of any psychotic disorder (mostly schizophrenia spectrum or non-affective psychosis) in people exposed to maternal age at birth <20 years or 30-34 years. A small, significant effect of decreased risk of psychotic disorders was found in people exposed to maternal age at birth between 20-29 years. There were small, significant effects of increased risk of psychotic disorders in people exposed to paternal age at birth <20 years or ≥35 years.

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Cheng JY, Ko JS, Chen RY, Ng EM

Meta-regression analysis using latitude as moderator of paternal age related schizophrenia risk: high ambient temperature induced de novo mutations or is it related to the cold?

Schizophrenia Research 2008; 99(1-3): 71-6

View review abstract online

Comparison	**Paternal age at birth and schizophrenia in adulthood, controlling for the possible confounders of increased latitude and low ambient temperature.**
Summary of evidence	**Moderate quality evidence (large samples, mostly inconsistent, imprecise, direct) suggests an increased risk for schizophrenia when paternal age is over 35 years, with risk increasing when paternal age is over 45 years.** **In the Northern hemisphere, this risk may increase slightly with increased latitude and decreased annual mean daily temperature, although these measures are indirect.**

Paternal age

Older paternal age is associated with small to medium-sized increased risk of schizophrenia in the offspring;

N = 3,155,007, 5 cohort studies (follow up between 16 and 31 years)

25 to 34 years vs. < 24 years: RR = 1.20, 95%CI 0.98 to 1.48, $p = 0.07$, $I^2 = 72.8\%$, $p < 0.01$

35 to 44 years vs. < 24 years: RR = 1.60, 95%CI 1.16 to 2.22, $p = 0.01$, $I^2 = 81.5\%$, $p < 0.01$

≥45 vs. < 24 years: RR = 2.01, 95%CI 1.43 to 2.83, $p = 0.01$, $I^2 = 63.9\%$, $p = 0.02$

All studies controlled for maternal age.

This effect was not found in the meta-analysis of case-control studies;

N = 210,652, 4 case-control studies

< 20 years vs. 20-24 years: RR = 1.03, 95%CI 0.88 to 1.21, $p = 0.68$, $I^2 = 0\%$, $p = 0.79$

25 to 34 years vs. 20-24 years: RR = 1.00, 95%CI 0.95 to 1.06, $p = 0.84$, $I^2 = 0\%$, $p = 0.62$

≥35 years vs. 20-24 years: RR = 1.43, 95%CI 0.94 to 2.18, $p = 0.09$, $I^2 = 69.2\%$, $p = 0.02$

Meta-regression shows no moderating effects of latitude of study site or annual mean daily temperature on paternal age-related risk for schizophrenia;

N = 210,652, 4 case-control studies

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Latitude; *B* = 0.01, 95%CI -0.01 to 0.02, *p* = 0.36 Annual mean daily temperature; *B* = - 0.02, 95%CI -0.05 to 0.01, *p* = 0.29 N = 3,155,007, 5 cohort studies Latitude; *B* = -0.01, 95%CI -0.01 to 0.01, *p* = 0.71 Annual mean daily temperature; *B* = 0.01, 95%CI -0.02 to 0.04, *p* = 0.59 *However, subgroup analysis removing one case-control study (Australian) as authors state season of birth effect has not been observed in the Southern hemisphere, reveal significant associations, with decreased annual mean daily temperature and increased latitude associated with increased paternal age-related risk for schizophrenia;* N = 210,392, 3 case-control studies Decreased annual mean daily temperature: *B* = -0.171, 95%CI -0.319 to -0.023, *p* = 0.023 Increased latitude: *B* = 0.083, 95%CI -0.001 to 0.167, *p* = 0.051

Consistency in results‡	Mostly inconsistent
Precision in results§	Precise
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 non-affective psychosis) in adulthood in people who were exposed to different parental ages at birth.**
Summary of evidence	**Moderate quality evidence (unclear sample size, some inconsistency, mostly precise, direct) finds small, significant effects of increased risk of psychotic disorders in people exposed to maternal age at birth <20 years or 30-34 years. A small, significant effect of decreased risk of psychotic disorders**

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	was found in people exposed to maternal age at birth 20-29 years. Small, significant effects of increased risk of psychotic disorders in people exposed to paternal age at birth <20 years or ≥35 years.
Maternal age	
A small, significant effect of increased risk of psychotic disorders in people exposed to maternal age at birth <20 years or 30-34 years; <20 years: 22 studies, N not reported, OR = 1.17, 95%CI 1.07 to 1.27, p = 0.0004, I^2 = 19%, p = 0.21 30−34 years: 20 studies, N not reported, OR = 1.05, 95%CI 1.01 to 1.09, p = 0.019, I^2 = 0%, p = 0.83 *A small, significant effect of decreased risk of psychotic disorders in people exposed to maternal age at birth 20-29 years;* 20−24 years: 20 studies, N not reported, OR = 0.93, 95%CI 0.89 to 0.96, p < 0.0001, I^2 = 0%, p = 0.83 25−29 years: 21 studies, N not reported, OR = 0.92, 95%CI 0.88 to 0.95, p < 0.0001, I^2 = 5%, p = 0.40 *No significant effect of;* ≥35 years: 24 studies, N not reported, OR = 1.44, 95%CI 0.98 to 2.12, p = 0.062, I^2 = 99%, p < 0.0001	
Paternal age	
A small, significant effect of increased risk of psychotic disorders in people exposed to paternal age at birth <20 years or ≥35 years; <20 years: 11 studies, N not reported, OR = 1.31, 95%CI 1.17 to 1.46, p < 0.0001, I^2 = 0%, p = 0.74 ≥35 years: 13 studies, N not reported, OR = 1.28, 95%CI 1.06 to 1.55, p = 0.012, I^2 = 97%, p < 0.0001 *No significant effect of;* 20−24 years: 12 studies, N not reported, OR = 0.97, 95%CI 0.91 to 1.04, p = 0.45, I^2 = 25%, p = 0.19 25−29 years: 12 studies, N not reported, OR = 0.96, 95%CI 0.83 to 1.11, p = 0.57, I^2 = 92%, p < 0.001 30−34 years: 12 studies, N not reported, OR = 0.97, 95%CI 0.94 to 1.00, p = 0.058, I^2 = 0, p = 0.98	
Consistency in results	Some inconsistency
Precision in results	Mostly precise

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Directness of results	Direct

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

View review abstract online

Comparison	**Maternal age at birth and schizophrenia in adulthood.**
Summary of evidence	**Moderate quality evidence (large samples, unable to assess consistency, imprecise, direct) suggests a medium to large increased odds of having a mother aged under 17 years, a small to medium increased odds of having a mother aged under 19 years, and a small increased odds of having a mother aged 20 to 30 years at birth for people with schizophrenia. There is a decreased odds with maternal age > 30 years.**

Maternal age

1 study (N = 21,059) reported a significant, small increased odds of having a mother aged 20 to 30 years at birth in people with schizophrenia compared to people without schizophrenia, with decreased odds > 30 years;

20 years: OR = 1.69, 95%CI 1.49 to 1.92, $p < 0.01$

20-25 years: OR = 1.43, 95%CI 1.34 to 1.52, $p < 0.01$

26-30 years: OR = 1.08, 95%CI 1.02 to 1.15, $p < 0.05$

31-35 years: OR = 0.78, 95%CI 0.73 to 0.83, $p < 0.01$

> 35 years: OR = 0.68, 95%CI 0.64 to 0.73, $p < 0.01$

1 study (N = 21,059) reported a significant, medium to large increased odds of having a mother aged under 17 years, and a small to medium effect under 19 years, with decreased risk of maternal age ≥ 40 years;

< 17 years: OR = 4.38, 95%CI 2.24 to 8.55, $p < 0.01$

< 19 years: OR = 1.71, 95%CI 1.30 to 2.24, $p < 0.01$

> 30 years: OR = 1.07, 95%CI 0.91 to 1.26, $p > 0.05$

≥ 40 years: OR = 1.77, 95%CI 1.04 to 3.00, $p < 0.05$

1 study (N = 1,002) reported no significant difference between maternal ages ≥ 19 years or ≥ 30 years and 20 to 29 years, after adjusting for sex, ages of other siblings, birth order, and paternal age; ≤ 19 years: OR = 0.8, 95%CI 0.4 to 1.7, *p* > 0.05 ≥ 30 years: OR = 1.2, 95%CI 0.8 to 1.8, *p* > 0.05 *1 study (N = 164) reported no significant difference between maternal ages ≥ 35 and < 35 years;* OR = 1.16, 95%CI 0.49 to 2.76, *p* > 0.05 *1 study (N = 16 847) reported no significant difference with maternal age > 34 years;* > 34 years: OR = 1.18, 95%CI 0.46 to 3.02, *p* > 0.05 *1 study (N = 117) reported no significant difference with maternal age < 26 years;* <26 years: OR = 2.69, 95%CI 0.86 to 8.46, *p* > 0.05

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

Miller B, Messias E, Miettunen J, Alaraisanen A, Jarvelin M, Koponen H, Rasanen P, Isohanni M, Kirkpatrick B

Meta-analysis of Paternal Age and Schizophrenia Risk in Male Versus Female Offspring

Schizophrenia Bulletin 2011; 37(5): 1039-47

View review abstract online

Comparison	**Assessment of the relationship between paternal age groups, sex in offspring and the risk of schizophrenia.**
Summary of evidence	**Moderate to high quality evidence (large samples, consistent, some imprecision, direct) suggests a small increased risk of schizophrenia when paternal age was over 35 years at birth, with risk greatest over 50 years (imprecise), compared to paternal age 25-29. There was also a small increased risk when paternal age was less than 25 years.**
Paternal age	
6 cohort and 6 case-control studies, total N = 4,969,122, all comparisons are against a group aged	

Parental age

25 to 29 years.

For paternal age < 25 years there is a very small, significant increased risk of schizophrenia;

RR = 1.06, 95%CI 1.01 to 1.11, p = 0.02, I^2 = 0%, p = 0.87

For males with paternal age < 25 years there is a very small, significant increased risk;

RR = 1.08, 95%CI 1.02 to 1.14, p = 0.01, I^2 = 0%, p = 0.97

For females with paternal age < 25 years there is no significant increased risk;

RR = 1.04, 95%CI 0.97 to 1.12, p = 0.28, I^2 = 0%, p = 0.90

For paternal age 30 to 34 years there is a very small, significant increased risk;

RR = 1.06, 95%CI 1.01 to 1.10, p = 0.02, I^2 = 0%, p = 0.48

For males with paternal age 30 to 34 years there is no increased risk;

RR = 1.03, 95%CI 0.97 to 1.08, p = 0.35, I^2 = 14.9%, p = 0.30

For females with paternal age 30 to 34 years there is a very small, significant increased risk;

RR = 1.10, 95%CI 1.03 to 1.19, p < 0.01, I^2 = 0%, p = 0.48

For paternal age 35 to 39 years there is a very small, significant increased risk;

RR = 1.13, 95%CI 1.08 to 1.19, p < 0.01, I^2 = 66.7%, p = 0.01

For males with paternal age 35 to 39 years there is a very small, significant increased risk;

RR = 1.12, 95%CI 1.06 to 1.19, p < 0.01, I^2 = 65.6%, p < 0.01

Authors report results are not significant with one study removed.

For females with paternal age 35 to 39 years there is a very small, significant increased risk;

RR = 1.12, 95%CI 1.03 to 1.23, p = 0.01, I^2 = 0%, p = 0.71

For paternal age 40 to 44 years there is a very small, significant increased risk;

RR = 1.22, 95%CI 1.14 to 1.30, p < 0.01, I^2 = 3.3%, p = 0.41

For males with paternal age 40 to 44 years there is a very small, significant increased risk;

RR = 1.21, 95%CI 1.11 to 1.32, p < 0.01, I^2 = 30%, p < 0.16

For females with paternal age 40 to 44 years there is a very small, significant increased risk;

RR = 1.24, 95%CI 1.10 to 1.38, p = 0.01, I^2 = 0%, p = 0.74

For paternal age 45 to 49 years there is a very small, significant increased risk;

RR = 1.21, 95%CI = 1.09 to 1.34, p < 0.01, I^2 = 67.9%, p < 0.01

For males with paternal age 45 to 49 years there is a very small, significant increased risk;

RR = 1.24, 95%CI = 1.09 to 1.41, p < 0.01, I^2 = 51.4%, p < 0.03

For females with paternal age 45 to 49 years there is a very small, significant increased risk;

RR = 1.22, 95%CI = 1.03 to 1.44, p = 0.02, I^2 = 73.8%, p < 0.01

Parental age

Authors report results are not significant with one study removed. *For paternal age ≥ 50 years there is a small significant increased risk;* RR = 1.66, 95%CI 1.46 to 1.89, $p < 0.01$, $I^2 = 77.8\%$, $p < 0.01$ *For males with paternal age ≥ 50 years there is a significant increased risk;* RR = 1.73, 95%CI 1.47 to 2.04, $p < 0.01$, $I^2 = 83.6\%$, $p < 0.01$ *For females with paternal age ≥ 50 years there is a small, significant increased risk;* RR = 1.61, 95%CI 1.30 to 1.99, $p = 0.01$, $I^2 = 69.5\%$, $p = 0.02$ Authors report results are not significant with one study removed. Effect sizes were similar for separate analyses of cohort and case–control studies.	
Consistency in results	Consistent
Precision in results	Precise, apart from ≥ 50 years, male/female subgroups.
Directness of results	Direct

Torrey EF, Buka S, Cannon TD, Goldstein JM, Seidman LJ, Liu T, Hadley T, Rosso IM, Bearden C, Yolken R H

Paternal age as a risk factor for schizophrenia: How important is it?

Schizophrenia Research 2009; 114(1-3): 1-5

View review abstract online

Comparison	**Paternal age groups; 35 years or older, 45 years or older and 55 years or older and risk of schizophrenia in adulthood.**
Summary of evidence	**Moderate quality evidence (direct, precise, assumed large samples based on previous reporting, consistency unsure) suggests a small increased risk of schizophrenia with paternal age over 35 years. Moderate to low quality evidence (imprecise) suggests risk is greatest if paternal age is 55 years or more.**
Paternal age	
10 large observational studies *For paternal age of ≥ 35 years, there is a small, significant increased risk;* OR = 1.28, 95%CI 1.11 to 1.48, p not reported, I^2 not reported	

Parental age

8 observational studies, N not reported *For paternal age of ≥ 45 years, there is no significant increased risk;* OR = 1.38, 95%CI 0.95 to 2.01, *p* not reported, I^2 not reported 5 large observational studies *For paternal age of ≥ 55 years, there is a medium size significant increased risk;* OR = 2.21, 95%CI 1.46 to 3.37, *p* not reported, I^2 not reported	
Consistency in results	Consistency measures not reported
Precision in results	Precise only for paternal age of ≥ 35 years
Directness of results	Direct measure of paternal age, direct comparisons

Wohl M, Gorwood P

Paternal ages below or above 35 years old are associated with a different risk of schizophrenia in the offspring

European Psychiatry 2007; 22(1): 22-6

View review abstract online

Comparison	**Paternal age groups, from < 20 to > 39 years, in increments of 5 years and risk of schizophrenia.**
Summary of evidence	**Moderate to high quality evidence (large samples, consistent for cohort studies, precise, direct) suggests a small, increased risk of schizophrenia with paternal age under 20 years or over 35 years, with the risk highest with paternal age over 54 years.**
Paternal age	

Parental age

Compared to paternal age 20 to 24 years, there is a small significant increased risk of schizophrenia with paternal age < 20 years;

7 studies, N = 1,103,231, OR = 1.49, CI and *p* not reported, Q*p* = 0.499

No differences between < 20 years and other age ranges.

Compared to paternal age < 25 years, there is a small significant increased risk or schizophrenia with paternal age > 34 years;

OR = 1.14, CI not reported, Q*p* = 0.001

Increasing to OR 5.87 with paternal age > 54 years and Q*p* = 0.739

Compared to paternal age < 35 years, there is a small significant increased risk with paternal age ≥ 35 years;

OR = 1.18, 95%CI 1.10 to 1.26, Q*p* = 0.0002

Compared to paternal age < 35 years, there was a significant increased risk of schizophrenia with paternal age ≥ 35 years;

3 case control studies, N = 203,116, OR = 1.13, 95%CI 1.03 to 1.25, Q*p* = 0.009

4 cohort studies, N = 900,115, OR = 1.49, 95%CI 1.12 to 1.99, Q*p* = 0.99

Consistency in results	Consistent for cohort studies
Precision in results	Precise
Directness of results	Direct

Explanation of acronyms

B or *b* = beta, regression coefficient, 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 = relative risk, 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.

† 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 the treatment group 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. 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 certain risk factor. An RR or OR of 1.00 means there is no difference between groups. A medium effect is considered if RR > 5 or < 0.2 and a large effect if RR > 2 or < 0.5[9]. lnOR stands for logarithmic OR where a lnOR of 0 shows no difference between groups.

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 moderate effect, and 0.8 and over represents a large treatment effect.

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 denominator. This denominator is the sum of individual units of time that the persons in the

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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[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.

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