TECHNICAL COMMENTARY

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SCHIZOPHRENIA LIBRARY

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 (systematic literature search, detailed methodology with inclusion/exclusion criteria) published in full text, in English, from the year 2000 that report results separately for people with a diagnosis of schizophrenia, schizoaffective disorder, schizophreniform disorder or first episode schizophrenia. Reviews were identified by searching the databases MEDLINE, EMBASE, CINAHL, Current Contents, PsycINFO and the Cochrane library. Hand searching reference lists of identified reviews was also conducted. When multiple copies of reviews were found, only the most recent version was included. Reviews with pooled data are given priority for inclusion.

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

- 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 suggests a medium to large increased risk of schizophrenia when maternal age was under 17 years at birth, a small to medium

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increased risk of schizophrenia with maternal age less than 19 years, and a small increased risk with maternal age 20 to 30 years. There was a decreased risk of schizophrenia with maternal age over 30 years.

Parental age

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

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	

Parental 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

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

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

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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 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.

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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, $p = 0.02$, $I^2 = 73.8\%$, $p < 0.01$ 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?

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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 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

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Parental age

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	
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.

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† 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[8]. 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 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[9].

‖ 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. Fekadu A, Shibre T, Cleare AJ (2010): Toxoplasmosis as a cause for behaviour disorders--overview of evidence and mechanisms. *Folia Parasitologica* 57: 105-13.
2. GRADEWorkingGroup (2004): Grading quality of evidence and strength of recommendations. *British Medical Journal* 328: 1490.
3. Cheng JY, Ko JS, Chen RY, Ng EM (2008): 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* 99: 71-6.
4. Torrey EF, Buka S, Cannon TD, Goldstein JM, Seidman LJ, Liu T*, et al.* (2009): Paternal age as a risk factor for schizophrenia: How important is it? *Schizophrenia Research* 114: 1-5.
5. Wohl M, Gorwood P (2007): Paternal ages below or above 35 years old are associated with a different risk of schizophrenia in the offspring. *European Psychiatry: the Journal of the Association of European Psychiatrists* 22: 22-6.
6. 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.
7. Miller B, Messias E, Miettunen J, Alaraisanen A, Jarvelin MR, Koponen H*, et al.* (2011): Meta-analysis of Paternal Age and Schizophrenia Risk in Male Versus Female Offspring. *Schizophrenia Bulletin* 37: 1039-47.
8. Rosenthal JA (1996): Qualitative Descriptors of Strength of Association and Effect Size. *Journal of Social Service Research* 21: 37-59.
9. GRADEpro (2008): [Computer program]. Jan Brozek, Andrew Oxman, Holger Schünemann. *Version 32 for Windows*.