Adoptive Paternal Age and Risk of Psychosis in Adoptees: A Register Based Cohort Study

Mats Ek*, Susanne Wicks, Cecilia Magnusson, Christina Dalman
Karolinska Institutet, Stockholm, Sweden

Abstract
The association between advancing paternal age and increased risk of schizophrenia in the offspring is well established. The underlying mechanisms are unknown. In order to investigate whether the psychosocial environment associated with growing up with an aged father explains the increased risk we conducted a study of all adoptive children in Sweden from 1955–1985 (n = 31 188). Their risk of developing schizophrenia or non-affective psychosis in relation to advancing age of their adoptive fathers’ was examined. We found no association between risk of psychoses and advancing adoptive paternal age. There was no support of psychosocial environmental factors explaining the “paternal age effect”.

Participants
The study population (n = 35 058) was identified via the Multi-Generation Register (held by Statistics Sweden). It consisted of all children adopted by Swedish families and born abroad in 1955–1985 or in Sweden during 1955–1984.

Adoptees from abroad were included if they had immigrated to Sweden before 2 years of age (n = 18 719).

Swedish adoptees were included if they had a known biological mother and two adoptive parents (n = 16 339). Excluded were individuals living with a biological parent at any 5 year point when they were 1–15 years old (n = 1337), not living in a family household (n = 257), or adopted by grandparents or siblings (n = 230).

Individuals from both groups of adoptees were excluded if they emigrated from Sweden or died before 18 years of age (n = 358), had an adoptive father less than 20 years of age (n = 23), or were not living with their adoptive father in the first possible Census (n = 1665).

The final sample consisted of 31 188 adopted children (13 405 born in Sweden and 17 783 born abroad).

The Register of Total Population (held by Statistics Sweden) provided data on emigration and date of death. Household and family data was obtained via linkage to the Swedish Population and Housing Censuses (held by Statistics Sweden).

Description of Procedures

Power. Power calculations showed an 80% chance to detect an increased relative risk for non-affective psychoses with advanced adoptive paternal age of 1.5 with 95% confidence.

Schizophrenia and Non-Affective Psychosis. The adopted individuals were followed in the National Patient Register (held by Statistics Sweden) from age 16 years to age 20 years.

The adopted individuals were followed in the National Patient Register (held by Statistics Sweden) from age 16 years to age 20 years. The adopted individuals were followed in the National Patient Register (held by Statistics Sweden) from age 16 years to age 20 years.
Paternal Age and Risk of Psychosis in Adoptees

295H] or ICD-10: F20) or any non-affective psychosis including schizophrenia (ICD-8: 295, 297, 290.20–290.99, 299.99; ICD-9: 295, 297, 298.0C-X or ICD-10: F20–F29).

Paternal age. The adoptive father’s age at the adoptees birth, derived from the Multi-Generation Register, was categorized into 4 groups: 20–29 years, 30–34 years, 35–39 years and ≥40 years. The group of fathers aged 30–34 years was chosen as reference group because of low numbers of fathers and few cases in the youngest group (20–29 years). There was information about both biological and adoptive paternal age among 24% of the sample (7588 Swedish-born adoptees).

Covariates. We considered the following covariates (described in more detail below): adoptees gender (female v. male) and place of birth (Sweden v. other country), advanced adoptive maternal age (≥35 years old v. <35 years old), adoptive paternal socioeconomic group, residence (urban v. non-urban), and adoptive parents in-patient treatment for psychiatric disorder (yes v. no).

Paternal socioeconomic group was divided into four groups and measured by the first possible census after the child’s birth. The data was derived from the Swedish Population and Housing Censuses where data on occupation was collected every 10 years from 1960 to 1990, with an additional measurement in the census of 1985. The groups were: 1. Non-manual employees including military (1960–1970: code 04, 06, 09; 1980–1990: code 33, 36, 46, 56, 57, 60), 2. Self-employed including upper-level executives (1960–1970: code 01, 03, 05; 1980–1990: code 79, 89), 3. Manual labor (1960–1970: code 02, 07, 08; 1980–1990: code 11, 12, 21, 22), and 4. Occupations that are not identified (1960–1970: code 10; 1980–1990: code 91), students and unemployed non-students (1960–70: code 11, 12; 1980–1990: code 91, 95–99), and people were data on occupation were missing.

Residence was defined by the adoptive father’s place of living in the first possible census after the child’s birth. The data was derived from the Swedish Population and Housing Censuses that was performed every five years from 1960 to 1990. Urban was defined as living in one of the three major Swedish urban areas: Stockholm (code 01 and 02), Malmo manufactured by CIRUS) or ICD-10: F20–F29).

Strengths and Limitations

Our cohort of adoptees was identified from the total Swedish population and the adoptees originated from all parts of the world.
The study compared adoptees to each other. The adoptees were placed in families with no regard to the age of their biological father, leaving the genetic risk as a random variable. Altogether, this study design is well suited to explore the role of the psychosocial environment in the association between advancing paternal age and risk of offspring psychosis. The study relies on register-based case ascertainment from the National Patient Register which have been validated and proved reliable for epidemiological studies [14–16].

A potential limitation is that families that are adopting may be different from other families. An adopting family needs approval by social services before they are allowed to adopt. This considered, serious life events in the families' e.g. somatic disorders and deaths are prone to happen in all families. In addition, adjustment for socioeconomic group did not affect the results. However, our measure of socioeconomic group was limited to the father’s occupation. There may be residual confounding by socioeconomic factors. Furthermore, the sample selection, including more affluent families than the general population may affect the external validity.

There is strong support in the literature of an increased risk of schizophrenia in the offspring associated with advancing paternal age [1–7]. The underlying mechanism is being debated. The hypothesis that the paternal age effect is due to de novo mutations has been strongly suggested by Malaspina et al [1] and supported by the results of a study showing that advancing paternal age is associated with sporadic rather than non-sporadic cases of schizophrenia [17]. Interestingly, a recent study showed that the father’s age accounts for nearly all the variation of mutations in a child’s genome [18]. Further evidence of the de novo hypothesis is the finding that the risk to develop schizophrenia is decreasing with advancing paternal age in siblings to individuals with schizophrenia [19]. However, the de novo hypothesis has been questioned by Petersen et al [8] who found, in a large sample of more than 2 million individuals, that it was not the father’s age per se, but the father’s age when having his first child that was important. This supports the hypothesis of genetic traits as an explanation of the paternal age effect, i.e. that late childbearing is associated with a genetic disposition for schizophrenia (although not clinically evident). There is also evidence that mothers with schizophrenia have children with aged fathers [7] once again supporting the genetic trait hypothesis. In summary, the underlying mechanisms of the “paternal age effect” are still uncertain, but the evidence supports a combination of trait and de novo mutations rather than psychosocial factors.

This is the first study trying to disentangle nature from nurture and examine whether there are signs of an environmental component in the increased risk of schizophrenia associated with advancing paternal age. We found no association between risk of psychoses and advancing adoptive paternal age. Thus, there was no support of psychosocial environmental factors explaining the “paternal age effect” in our study. However, further studies are needed to rule this out.

Author Contributions
Conceived and designed the experiments: ME SW CM CD. Performed the experiments: ME SW. Analyzed the data: ME SW CM CD. Wrote the paper: ME SW CM CD.

Table 1. Odds ratios for schizophrenia and all non-affective psychosis in adopted children in relation to the adoptive paternal age.

| Paternal age | Analytic sample | Schizophrenia | All non-affective psychosis |
|--------------|----------------|---------------|-----------------------------|
|              | Adoptive       | Crude<sup>a</sup> | Adj<sup>b</sup> | Crude<sup>a</sup> | Adj<sup>b</sup> |
|              | n = 31 188     | n = 131       | OR 95% CI | OR 95% CI | n = 371 | Crude<sup>a</sup> | OR 95% CI | Adj<sup>b</sup> | OR 95% CI |
| 20–29        | 4,952          | 19            | 14.5% | 0.9 | 0.5–1.4 | 0.9 | 0.5–1.5 | 63 | 17.0% | 1.0 | 0.7–1.3 |
| 30–34        | 11,900         | 51            | 38.9% | 1.0 | reference | 1.0 | reference | 148 | 39.9% | 1.0 | reference |
| 35–39        | 9,552          | 35            | 26.7% | 0.8 | 0.5–1.2 | 0.8 | 0.5–1.2 | 92 | 24.8% | 0.7 | 0.6–1.0 |
| ≥40          | 4,782          | 26            | 19.8% | 0.9 | 0.6–1.5 | 1.0 | 0.6–1.6 | 68 | 18.3% | 1.0 | 0.7–1.3 |

<sup>a</sup>Adjusted for birth date.
<sup>b</sup>Adjusted for birth date, gender, place of birth and paternal occupational class.

CI = Confidence Interval.

OR = Odds Ratio.

doi:10.1371/journal.pone.0047334.t001

References
1. Malaspina D, Harlap S, Fennig S, Heiman D, Nahon D, et al. (2001) Advancing paternal age and the risk of schizophrenia. Arch Gen Psychiatry 58: 361–367.
2. Dalman C, Allebeck P (2002) Paternal age and schizophrenia: further support for an association. Am J Psychiatry 159: 1591–1592.
3. Brown AS, Schaefer CA, Wyatt RJ, Begy MD, Goetz R, et al. (2002) Paternal age and risk of schizophrenia in adult offspring. Am J Psychiatry 159: 1528–1533.
4. Zammit S, Allebeck P, Dalman C, Lundberg I, Hemmingsson T, et al. (2003) Paternal age and risk of schizophrenia. Br J Psychiatry 183: 405–408.
5. Byrne M, Agerbo E, Ewald H, Eaton WW, Mortensen PB (2003) Parental age and risk of schizophrenia: a case-control study. Arch Gen Psychiatry 60: 673–678.
6. Sipos A, Rasmussen F, Harrison G, Tyellin P, Lewis G, et al. (2004) Paternal age and schizophrenia: a population based cohort study. Br J 29: 1070.
7. Miller B, Suvisaari J, Miettunen J, Jarvelin MR, Haucka J, et al. (2011) Advanced paternal age and parental history of schizophrenia. Schizophr Res 133: 125–132.
8. Petersen L, Mortensen PB, Pedersen CB (2011) Paternal age at birth of first child and risk of schizophrenia. Am J Psychiatry 168: 82–88.
9. Perrin MC, Brown AS, Malaspina D (2007) Aberrant epigenetic regulation could explain the paternal age effect on schizophrenia. Schizophr Bull 33: 1270–1273.
10. Morgan C, Kirkbride J, Leff J, Craig T, Hutchinson G, et al. (2007) Parental separation, loss and psychosis in different ethnic groups: a case-control study. Psychol Med 37: 493–503.
11. Agid O, Shapiro R, Zilnin J, Ritsner M, Hanin B, et al. (1999) Environment and vulnerability to major psychiatric illness: a case control study of early parental loss in major depression, bipolar disorder and schizophrenia. Mol Psychiatry 4: 163–172.
12. Mortensen PB, Pedersen CB, Melbye M, Mors O, Ewald H (2003) Individual and familial risk factors for bipolar affective disorders in Denmark. Arch Gen Psychiatry 60: 1209–1215.
13. Miller B, Messias E, Miettunen J, Alaraissanen A, Jarvelin MR, et al. (2010) Meta-analysis of Paternal Age and Schizophrenia Risk in Male Versus Female Offspring. Schizophren Bull.

14. Dahlman C, Broms J, Cullberg J, Allebeck P (2002) Young cases of schizophrenia identified in a national inpatient register—are the diagnoses valid? Scand Psychiatry 37: 527–531.

15. Ekholm B, Ekholm A, Adolfsson R, Vares M, Osby U, et al. (2005) Evaluation of diagnostic procedures in Swedish patients with schizophrenia and related psychoses. Nord J Psychiatry 59: 457–464.

16. Ludvigsson JF, Andersson E, Ekbom A, Feychting M, Kim JL, et al. (2011) External review and validation of the Swedish national inpatient register. BMC Public Health 11: 450.

17. Malaspina D, Corcoran C, Fahim C, Berman A, Harkavy-Friedman J, et al. (2002) Paternal age and sporadic schizophrenia: evidence for de novo mutations. Am J Med Genet 114: 299–303.

18. Kong A, Frigge ML, Masson G, Bensenbacher S, Sulem P, et al. (2012) Rate of de novo mutations and the importance of father’s age to disease risk. Nature 488: 471–475.

19. Svensson AC, Lichtenstein P, Sandin S, Oberg S, Sullivan PF, et al. (2012) Familial aggregation of schizophrenia: The moderating effect of age at onset, parental immigration, paternal age and season of birth. Scand J Public Health 40: 43–50.