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Advanced paternal age and vulnerability to psychotic-like experiences in the offspring

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ABSTRACT

Objective: To investigate whether advanced paternal age is associated with increased psychotic-like experiences (PLEs) and increased sensitivity to Cannabis in the offspring.
Methods: A cross-sectional population-based study in 1684 participants aged 18 to 25.
Results: We found no association of paternal age with PLEs. Only the positive dimension subscale was associated to paternal age, but that could be largely contributed to outliers. Also no increased sensitivity to Cannabis smoking was apparent.
Conclusion: In the general population, we did not find robust support for an association between paternal age and vulnerability to PLEs in 18–25 year old offspring.

1. Introduction

Advanced paternal age at time of conception is considered a possible risk factor for developing psychotic disorders in the offspring (Malaspina et al., 2001, 2002; Byrne et al., 2003; Sipos et al., 2004; Buizer-Voskamp et al., 2011; Petersen et al., 2011). Whereas several studies show an association between advanced paternal age and schizophrenia in the offspring, it is less clear whether this constitutes a general increase in psychosis vulnerability, or a specific risk to a clinical psychiatric disorder. If psychosis vulnerability in the offspring increases with advancing paternal age in the general population, then this may be reflected in higher number of psychotic-like experiences (PLEs) (Poulton et al., 2000; Hanssen et al., 2005; Welham et al., 2009) and increased vulnerability to Cannabis.

To date, few studies have focused on the influence of advanced paternal age on PLEs in the offspring. Zammit et al. (2008) studied this relationship in 4531 participants and examined two outcomes: 1. suspected or definite symptoms and 2. definite symptoms only. They found, only when the model was adjusted for age of the other parent, an increased risk of symptoms with advancing paternal age in the first, broad definition group. No association was apparent for the group with definite symptoms. However, considering that the mean age of participants in this study was only 12.9 years, possibly, a study in older probands could detect the presence of more PLEs.

We therefore studied the association of advanced paternal age and PLEs in a population at the most vulnerable age; adolescence and young adulthood. We hypothesized that advanced paternal age is associated with PLEs in the offspring, as measured using the Community Assessment of Psychic Experiences (CAPE). Moreover, since Cannabis use is a well-known risk factor associated with both psychosis and PLEs (Tennant and Groesbeck, 1972; Chopra and Smith, 1974; Schubart et al., 2010; Kuepper et al., 2011; van Gastel et al., 2012) we hypothesized that advanced paternal age is also reflected in an enhanced sensitivity to Cannabis in the offspring: implying that regular Cannabis use increases the risk of PLEs more in the offspring of older fathers than in the general population.

2. Methods

2.1. Participants and study design

The sample for this cross-sectional study consisted of 1820 participants between the ages of 18 and 25 years. They were recruited by (online) advertisements, chat-programs, college intranet and 'coffeeshops' (shops selling Cannabis products). The measurements were obtained using a website directed towards adolescents and young adults (www.cannabisquest-community.nl). From June 2006 until February 2010 participants filled out the online questionnaires. The chance of winning several prizes for filling out the questionnaires was used as an incentive. Information was not submitted anonymously and participants consented to the possibility of being contacted

Abbreviations: PLEs, psychotic-like experiences; CAPE, Community Assessment of Psychic Experiences.

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later for follow-up. The study was approved by the University Medical Center Utrecht medical ethical commission and all participants gave online informed consent.

2.2. Instruments

PLEs were assessed by the Community Assessment of Psychic Experiences (CAPE). This self-report questionnaire presents a total number of PLEs as total score and distinguishes three subscales: positive symptoms, negative symptoms and depressive symptoms (Stefanis et al., 2002).

In The Netherlands, THC concentration and the price of Cannabis are highly correlated (Niesink et al., 2009). Therefore, the amount of euros spent on Cannabis was used as an estimation of the amount of Cannabis and particularly, the amount of THC, participants use. We calculated a dichotomous variable, in which participants who spent 0 to 3 euros per week in the last month were considered as non-regular users and participants who spent 3 euros or more per week in the last month were regarded regular users. This cut-off score was used for two reasons. Firstly, the data showed a suitable distribution: 66% of the participants spent 0 to 3 euros per week and 34% spent 3 euros or more per week. Moreover, previous studies show that Cannabis use equivalent of 3 euros or more per week is associated with increased risk of PLEs (Schubart et al., 2010).

Parental age was calculated based on birth year of the parent and handled as a continuous variable.

2.3. Data analysis

To assess the relationship of paternal age on frequency of PLEs, an analysis of covariance was used adjusting for age of the participant, gender and age difference between parents (maternal age difference). Since maternal age is highly correlated with paternal age, we used the age difference between parents which we named 'maternal age difference' (that is less correlated with paternal age) as a covariate instead. To further examine the influence of paternal age on the positive, negative and depressive subscales of the CAPE, a multivariate analysis of covariance (MANCOVA) was applied with these subscales as dependents and the paternal age and the covariates as independents.

Sensitivity to Cannabis was investigated by examining the interaction of paternal age and Cannabis use with total frequency of PLEs as the outcome in a similarly adjusted model.

Finally, we calculated the effect sizes for 95% power in this design using G*Power (Erdfeler et al., 1996).

2.4. Missing data

Of the total sample of 1820 subjects, data of either one of the independent variables was missing in 127 cases. Nine participants were excluded based on incredible answers regarding the parental age at time of birth of the proband (below 13 or above 65). After casewise deletion and exclusion of 9 subjects, a sample of 1684 subjects remained.

3. Results

3.1. Total frequency of PLEs and CAPE subscales

We found no association between paternal age and total frequency of PLEs. Also, no effect of paternal age on sensitivity to Cannabis in the offspring was found. See Table 1 for descriptives and full results.

However, paternal age was positively associated with positive symptoms ($F_{1,1683} = 4.15$, $p = 0.042$) but not with the other subscales (negative and depressive) in the offspring. Furthermore, no overall interaction of paternal age with regular Cannabis use on CAPE subscales was found.

Table 1
Characteristics of the participants and association with PLEs frequency (N = 1684).

	Mean (sd) or %	Association with PLEs frequency F(1,1683), p
Paternal age	31.78 (5.24)	0.018, *0.893*
Regular Cannabis use	34.0%	8.023, *0.005**
Age of participant	20.80 (2.11)	1.284, *0.257*
Maternal age difference	2.37 (3.80)	4.250, *0.039**
Gender (% male)	49.5%	14.071, *<0.001**
Regular Cannabis use * paternal age		0.931, *0.335*

* Significant; $p \leq 0.05$.

Analysis showed we had 95% power to detect effect sizes of $f \geq 0.09$ (classifying as small effects) with an alpha level of 0.05.

3.2. Analysis of outliers

Despite the fact that none of the participants fulfilled the criteria for outliers by Cook's distances, 13 parents were under the age of 18 at time of birth of the proband (exceeding 3 times standard deviation) including 2 fathers and 4 mothers aged 15 and younger. To ensure results were not biased by these outliers, we performed a second analysis in which we excluded the participants with these young parents (five fathers and eight mothers). The results remained unchanged with respect to most outcomes: PLEs frequency ($F_{1,1670} = 0.009$, $p = 0.924$), CAPE subscales: depressive ($F_{1,1670} = 0.128$, $p = 0.720$), negative ($F_{1,1670} = 2.216$, $p = 0.137$) and Cannabis sensitivity: paternal age * Cannabis ($F_{1,1670} = 0.293$, $p = 0.588$). However, the association of paternal age with CAPE positive subscale was no longer significant ($F_{1,1670} = 2.694$, $p = 0.101$).

4. Discussion

In this large cross-sectional study we did not find an association between paternal age and the frequency of psychotic-like experiences (PLEs) in the offspring. Further analyses revealed a small but significant association between positive symptoms and paternal age that was largely based on the presence of outliers with parents younger than 18. The interaction between paternal age and Cannabis use was not associated with the frequency of PLEs, implying that in the offspring of older fathers regular Cannabis use does not increase the risk of PLEs more than in the general population. Our negative findings are partly in line with previous reports on PLEs in younger participants (Zammit et al., 2008). Whereas Zammit and colleagues showed weak evidence for an association of paternal age with PLEs in the offspring, this association only existed in an adjusted model in the broad symptom group. Our data suggest that the association of paternal age with PLEs in the offspring is not robust in the general population. Moreover, the strong influence of a small group of participants with very young parents is noteworthy in light of earlier studies that also may have included parents under the age of 18 (Malaspina et al., 2001, 2002; Byrne et al., 2003; Sipos et al., 2004) and further study seems warranted.

The cross-sectional web-based design of the study has facilitated the substantial sample size and small number of missing data. It comes at the cost of less control on possible sources of bias such as selection, intoxication, and validity of internet assessment. Although we cannot rule out the influence of these sources, there is also no reason to assume it is any different in the offspring of older parents and have led to bias. Furthermore, the power of the study is unlikely to have been of major limitation, since analysis showed that we had excellent power to detect very small effect sizes.

Overall we did not find support for an association between paternal age and PLEs in the offspring in a large sample of 18–25 years old participants drawn from the general population. Furthermore, no increased sensitivity to Cannabis in the offspring of older fathers was apparent. Our results therefore suggest that advanced paternal age is

not associated with increased general susceptibility to psychosis in the offspring. Instead, the association of paternal age may be specifically with clinical psychiatric disorders in the offspring.

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Contributors

Annabel Vreeker was involved in collecting and analyzing the data and drafting the paper.

Christian Schubart was involved in the conceptualization and design of the study and critical revision after the draft.

Willemijn van Gastel was involved in the conceptualization and design of the study and critical revision after the draft.

René Kahn was involved in the design of the study, interpretation of the data, revision of the draft and supervision of the project.

Marco Boks was involved in the design of the study, interpretation of the data, revision of the draft and supervision of the project.

Conflict of interest

None of the authors has any conflict of interest.

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