

Advancing paternal age and psychiatric disorders

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Age of first and subsequent parenthood has been increasing all over the world. From a public health perspective, it is becoming apparent that this shift might have negative consequences. When considering the potential negative effects of late parenthood, focus has traditionally been on older maternal age, which has been associated with multiple adverse outcomes in the offspring (1). More recently, however, the offspring of older fathers have been shown to have increased risk for a wide range of adverse health conditions, including psychiatric disorders.

These findings received considerable attention because they challenge traditional views on male fertility and reproduction. However, research findings on the links between advancing paternal age and psychiatric disorders have not always been replicable, and the mechanism or mechanisms behind the paternal age effect remain unclear, adding to the controversies around the findings.

In this paper we provide an updated overview of the research on the association between advancing paternal age and psychiatric disorders in the offspring and discuss potential biological and social mechanisms.

SCHIZOPHRENIA

Studies dating back to as early as 1958 have shown associations between advanced paternal age and schizophrenia (2). The first modern era study was published in 2001 and reported that, compared with offspring of fathers younger than 25 years, the relative risk (RR) of schizophrenia in offspring of men aged 45 to 49 and 50 years or more was 2.02 (95% CI: 1.17-3.51) and 2.96 (95% CI: 1.60-5.47), respectively (3).

Since then, several studies have replicated these findings, yet negative results have also been reported. Potential confounding factors such as maternal age, parity of the mother, socioeconomic status, birth order, family history of psychiatric disorders, and urbanicity have been examined. A meta-analysis published in 2011, including 6 cohort studies and 6 case-control studies, found that the RR for schizophrenia in offspring of fathers aged ≥ 50 years was 1.66 (4).

AUTISM

In 1970, it was first suggested that there is a link between older paternal age and autism (5). Since then, numerous studies have found associations between autism spectrum disorders and/or infantile autism/autistic disorder and ad-

vancing paternal age. The results have been replicated in independent samples all over the world. The association between autism risk and paternal age is therefore robust, although the magnitude of this association has varied greatly.

A meta-analysis on paternal age and autism risk showed that offspring of men aged 50 years or older were 2.2 times more likely to have autism than offspring of men younger than 30 years, after controlling for maternal age and other documented risk factors for autism (6).

OTHER PSYCHIATRIC DISORDERS

Frans et al (7) reported a link between paternal age >55 and bipolar disorder (OR=1.37, 95% CI: 1.02-1.84). The association was strongest for individuals with an early onset of the disorder (<20 years) (OR=2.63). There have also been reports of an association between advancing paternal age and eating disorders (8), attention-deficit/hyperactivity disorder (9) and substance use problems (9).

In addition to psychiatric disorders, advancing paternal age has also been linked to impairments in the general cognitive ability (10), educational outcomes (9) and violent offending (11).

GRANDPATERNAL AGE

Interestingly, two recent studies using the Swedish multi-generational register showed an effect of advancing grandpaternal age on risk for schizophrenia (12) and autism (13), suggesting that age-associated effects may be transmitted across generations.

HOW OLD IS OLD?

There is no universally accepted definition of advanced paternal age but, within genetic counseling for congenital disorders, advanced paternal age is often defined as 40 years and older (14). However, there is no consistent evidence for a dramatic increase in risk for these disorders in offspring of fathers over 40. Instead, the risk increases linearly with paternal age. Therefore, at present, a cut-off at 40 years has no known underlying biological foundation.

Similarly, studies on schizophrenia and autism show no evidence of a threshold effect. Although the risk increase is

not necessarily linear, studies on the relation between paternal age and psychiatric disorders show no consistent evidence for a threshold age where the risk increases dramatically.

PROPOSED MECHANISMS UNDERLYING THE PATERNAL AGE EFFECT

The mechanisms underlying the association between paternal age and psychiatric disorder remain unclear. There are, however, several hypothesized mechanisms. Some hypotheses suggest that there is a causal link, while others argue that the associations can be explained by unmeasured confounding.

De novo mutations

It has been most frequently suggested that the association between advancing paternal age and psychiatric disorders is due to an increased burden of *de novo* mutations in germ cells of older men.

Women are born with their full supply of oocytes, and their meiosis is halted at metaphase II until fertilization. In contrast, male germ cells are produced continuously through reproductive life. More specifically, spermatogonial cells replicate every 16th day, resulting in approximately 200 divisions by the age of 20 years and 660 divisions by the age of 40 years (15). Each time the cell divides, the replication of the genome introduces the possibility of copy-error mutations. As a result of the large number of cell divisions during spermatogenesis, the mutation rate for base substitutions is much higher in men than in women, and increases with paternal age (16). These mutations may be inherited to the offspring and potentially have negative effects on their health.

Although it remains unclear whether new mutations are causing the relation between advancing paternal age and psychiatric disorders or other complex traits, it is possible that mutations are of great etiological importance for mental health. Brain function depends on the functionality of a very high number of genes and non-coding regulatory regions, and therefore the mutational target size is large.

Recent studies using exome sequencing methods confirmed that *de novo* point mutations have a role in the etiology of schizophrenia and autism (17-22). Moreover, Kong et al (18) found that fathers, on average, pass on to their offspring 25 new point mutations at age 20, increasing to 65 mutations at age 40. The study concluded that the mean number of *de novo* mutations in human spermatozoa increases by around 2 per year.

Epigenetic alterations

Modifications in gene expression that are not caused by changes to DNA sequence are referred to as epigenetic alter-

ations. They are mediated principally through changes in DNA methylation and chromatin structure. Although epigenetic features are reversible, it has been suggested that they can by structural inheritance be transmitted to offspring.

Perrin et al (23) and Sipos et al (24) have suggested that epigenetic alterations that occur as paternal age advances may be causally related to the susceptibility to schizophrenia in offspring. Animal models have documented DNA methylation changes associated with paternal age (25). Interestingly, paternal exposure to toxins and nutritional state, as well as age, have been found to influence the development in offspring and sometimes even development of grand-offspring (26).

Characteristics of older fathers

It is also possible that some of the environmental characteristics associated with older fatherhood increase the risk of psychiatric disorder. Some features of men who became first-time fathers at an older age were recently described in a Norwegian population-based study. The study showed that both higher and lower socioeconomic status groups were overrepresented among older fathers compared to younger fathers. Older fathers were also more likely to engage in negative health behavior and have poorer health (27). However, Ek et al (28) found no association between risk of psychoses and advancing adoptive paternal age, thus not supporting a role of psychosocial environmental factors in explaining the paternal age effect.

Selection into late fatherhood

It has also been suggested that the association between paternal age at birth and psychiatric disorder in offspring is confounded by psychiatric disorders or a genetic liability for psychiatric disorders in the father (29,30). Individuals with genes predisposing for psychiatric illness are more likely to have children with similar disorders. If a genetic liability for psychiatric disorders is also associated with a selection into late fatherhood, this would result in a non-causal association between paternal age and psychiatric disorders in the child. Similarly, if women with a genetic liability for psychiatric disorders tend more to have children with older men, this mating pattern could result in an association between late fatherhood and disorders in the children.

A study from Finland showed that advancing paternal age was associated with schizophrenia in the mother, but not in the father (31). However, other studies do not support this notion. Sibling-comparison studies offer rigorous control for familial confounding factors, including familial liability of psychiatric disorders. While multiple studies support a paternal age effect in autism (6,9,32), results of sibling analyses for schizophrenia have been inconclusive (6,30).

CONCLUSIONS

Advancing paternal age has been associated with a range of psychiatric disorders, with the strongest evidence in autism and schizophrenia. It has also been associated with other adverse neuropsychiatric outcomes. However, the mechanisms behind these associations remain unclear.

Multiple epidemiological study designs and molecular genetic studies, potentially combined with animal studies, could provide the necessary knowledge about the mechanisms that mediate the paternal age effect. The exploration of epigenetic mechanisms and how risk can be transmitted across generations is critical for understanding the etiology behind the paternal age effect. This knowledge might have important implications for clinicians, researchers, those affected by the disorders, and the general public.

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