



**Karolinska
Institutet**

Institutionen för medicinsk epidemiologi och biostatistik

HIGH PATERNAL AGE AND RISK OF PSYCHIATRIC DISORDERS IN OFFSPRING

AKADEMISK AVHANDLING

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ABSTRACT

Parental ages at childbirth are increasing all over the world and later parenthood might have negative health outcomes for the offspring. During recent year, numerous studies report links between and high paternal age and psychiatric disorders such as schizophrenia and autism. However, the knowledge about this association is limited. The aim of this thesis was to gain valuable knowledge about the paternal age effect regarding its specificity, transmission and mechanism. The studies were conducted in an epidemiological setting by using multiple large population-based data sources that also enable controlling for a range of documented risk factors including parental, perinatal and socioeconomic variables.

In our first study we reported, for the first time, that high paternal age also is associated with bipolar disorder. The risk increased monotonically with age of the father and was, compared to younger men, highest in offspring of men in the oldest age category including men aged 55 years and older (odds ratio = 1.37) after adjustments. It was also evident that the paternal age effect was stronger when only analyzing individuals with an early disorder onset.

In study II, we confirmed an association between advancing paternal age and autism in the offspring. More importantly, we found an association between advancing paternal age and autism risk in the grandchild. Compared to younger fathers, men who fathered a daughter when they were 50 years or older were 1.79 times more likely to have a grandchild with autism, and men who father a son at 50 years of age or older were 1.67 times more likely to have an affected grandchild.

An increased burden of rare copy number variants (CNVs) has been found in individuals with schizophrenia and it has been suggested that CNVs can arise during replication. In study III, we used a sample consisting of individuals affected with schizophrenia and matched controls and examined paternal age in relation to rare CNVs. Although we found that rare CNVs were more common in individuals with schizophrenia and that their fathers were on average 0.75 years older than controls, we found no association between rare CNVs and paternal age.

In study IV, twin analyses showed that late fatherhood defined as becoming a father at age 40 years or above is under genetic influence (heritability = 0.33). However, a genetic liability for psychiatric disorders in men or their spouse was not associated with later fatherhood. Instead, a genetic liability for these disorders was generally associated with men having children at younger ages.

In conclusion, this thesis provides valuable knowledge about advanced paternal age as a risk factor for psychiatric disorders and might have important implications for clinicians, researchers, and those affected by the disorders.