Older Fathers, Worse Psychiatric and Educational Outcomes

By Barbara Geller, MD reviewing D'Onofrio BM et al. JAMA Psychiatry 2014 Feb 26.

Results from a large, carefully performed epidemiological study

A greater number of de novo mutations, as occurs in sperm of older men, is associated with higher rates of autism spectrum disorders (ASD) in offspring (Nat Rev Genet 2014; 15:133). To further investigate the relationship of advanced paternal age to other psychiatric disorders and academic achievements, researchers used Swedish registries of all children born between 1973 and 2001 (N=2,615,081). Comparisons among siblings, cousins, and first-born cousins controlled for genetic and environmental factors.

In sibling analyses, paternal age 45 or higher at birth compared with paternal age 20 to 24 was associated with significantly greater risks for the following:

- ASD, hazard ratio (HR), 3.45
- Attention-deficit/hyperactivity disorder (ADHD), HR, 13.13
- Psychosis, HR, 2.07
- Bipolar disorders, HR, 24.70
- Suicide attempts, HR, 2.72
- Substance use problems, HR, 2.44
- Failing grades, OR, 1.59
- Low educational attainment, OR, 1.70

The hazard ratio can be interpreted as the chance of an event occurring. For example, a hazard ratio of 3.45 means that children whose fathers were older had almost three-and-a-half times more chance of having an autism spectrum disorder (ASD) than children whose fathers were younger.

http://en.wikipedia.org/wiki/Hazard_ratio

Sensitivity analyses among cousins and first-born cousins yielded similar results.

See original report: http://www.jwatch.org/na33882/2014/03/05/older-fathers-worse-psychiatric-and-educational-outcomes#sthash.GLyS3zUk.dpuf

Comment

Among the study's limitations, diagnoses (except for ADHD and ASD) relied on inpatient records, even though outpatient treatment of bipolar and other psychotic disorders has been increasing. Also, the study included premature infants (ages, ≥23 weeks), who are at greater risk for mental and intellectual disorders (JAMA Psychiatry 2013; 70:1231).

Even with these provisos, this study demonstrates strikingly higher risks for children's mental disorders at advanced paternal age. Furthermore, the sibling design obviates the need for data on parenting behaviors of older versus younger fathers. If patients ask, freezing sperm at a young age is currently problematic to recommend because the risks of assisted reproduction are not yet known (NEJM JW Psychiatry Sep 10 2012).

ORIGINAL ARTICLE ABSTRACT

Paternal Age at Childbearing and Offspring Psychiatric and Academic Morbidity

Brian M. D'Onofrio, PhD[1]; Martin E. Rickert, PhD[1]; Emma Frans, MSc[2]; Ralf Kuja-Halkola, MSc[2]; Catarina Almqvist, MD[2,3]; Arvid Sjölander, PhD[2]; Henrik Larsson, PhD[2]; Paul Lichtenstein, PhD[2]

[1]Department of Psychological and Brain Sciences, Indiana University, Bloomington
[2]Department of Medical Epidemiology and Biostatistics, Karolinska Institutet, Stockholm, Sweden
[3]Lung and Allergy Unit, Astrid Lindgren Children's Hospital, Stockholm, Sweden

JAMA Psychiatry. 2014;71(4):432-438. doi:10.1001/jamapsychiatry.2013.4525.

Importance

Advancing paternal age is associated with increased genetic mutations during spermatogenesis, which research suggests may cause psychiatric morbidity in the offspring. The effects of advancing paternal age at childbearing on offspring morbidity remain unclear, however, because of inconsistent epidemiologic findings and the inability of previous studies to rigorously rule out confounding factors.

Objective

To examine the associations between advancing paternal age at childbearing and numerous indexes of offspring morbidity.

Design, Setting, and Participants

We performed a population-based cohort study of all individuals born in Sweden in 1973-2001 (N = 2 615 081), with subsets of the data used to predict childhood or adolescent morbidity. We estimated the risk of psychiatric and academic morbidity associated with advancing paternal age using several quasi-experimental designs, including the comparison of differentially exposed siblings, cousins, and first-born cousins.

Exposure

Paternal age at childbearing.

Main Outcomes and Measures

Psychiatric (autism, attention-deficit/hyperactivity disorder, psychosis, bipolar disorder, suicide attempt, and substance use problem) and academic (failing grades and low educational attainment) morbidity.

Results

In the study population, advancing paternal age was associated with increased risk of some psychiatric disorders (eg, autism, psychosis, and bipolar disorders) but decreased risk of the other indexes of morbidity. In contrast, the sibling-comparison analyses indicated that advancing paternal age had a dose-response relationship with every index of morbidity, with the magnitude of the associations being as large or larger than the estimates in the entire population. Compared with offspring born to fathers 20 to 24 years old, offspring of fathers 45 years and older were at heightened risk of autism (hazard ratio [HR] = 3.45; 95% CI, 1.62-7.33), attention-deficit/hyperactivity disorder (HR = 13.13; 95% CI, 6.85-25.16), psychosis (HR = 2.07; 95% CI, 1.35-3.20), bipolar disorder (HR = 24.70; 95% CI, 12.12-50.31), suicide attempts (HR = 2.72; 95% CI, 2.08-3.56), substance use problems (HR = 2.44; 95% CI, 1.98-2.99), failing a grade (odds ratio [OR] = 1.59; 95% CI, 1.37-1.85), and low educational attainment (OR = 1.70; 95% CI, 1.50-1.93) in within-sibling comparisons. Additional analyses using several quasi-experimental designs obtained commensurate results, further strengthening the internal and external validity of the findings.

Conclusions and Relevance

Advancing paternal age is associated with increased risk of psychiatric and academic morbidity, with the magnitude of the risks being as large or larger than previous estimates. These findings are consistent with the hypothesis that new genetic mutations that occur during spermatogenesis are causally related to offspring morbidity.