

NEWS

The link between parental age and autism, explained

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29 NOVEMBER 2017



Older men and women are more likely than young ones to have a child with autism, according to multiple studies published in the past decade. Especially when it comes to fathers, this parental-age effect is one of the most consistent findings in the epidemiology of autism.

The link between a mother's age and autism is more complex: Women seem to be at an increased risk both when they are much older and much younger than average, according to some studies.

Nailing down why either parent's age influences autism risk has proved difficult, however.

How do we know that older men are at elevated risk of fathering a child with autism?

Epidemiologists have gathered data on large numbers of families and calculated how often men of different ages have a child with autism. The first rigorous study of this type, published in 2006, drew on medical records of **132,000 Israeli adolescents**. It showed that men in their 30s are 1.6 times as likely to have a child with autism as men under 30. Men in their 40s have a sixfold increase in risk.

Since then, scientists have conducted similar analyses of data on children born in **California, Denmark** and **Sweden**, as well as of an **international dataset on 5.7 million** children. Nearly all of this research has shown an increased prevalence of autism among the children of older fathers.

At what age does the risk increase for men?

No one knows. The age ranges and ages of the men differ across studies, making their results hard to compare. Overall, the findings indicate that the risk increases steadily over time rather than suddenly rising after a certain age.

How big is the increase in risk?

The results of studies vary from 5 to 400 percent. One 2017 study based on whole-genome **sequencing of nearly 5,000 people** suggests that parents in their mid-40s are 5 to 10 percent more likely to have a child with autism than are 20-year-old parents.

But a large 2014 study based on Swedish medical records hinted that the risk of autism among children born to fathers older than 45 is about **75 percent higher** than it is for children born to fathers in their early 20s. And a 2010 analysis of Swedish data found that men over 55 are **four times as likely** to have a child with autism as men under 30.

Even so, the absolute risk of having a child with autism is **low even for the oldest parents**. The researchers in the 2017 study calculated that about 1.5 percent of children born to parents in their 20s will have autism, compared with about 1.58 percent of children born to parents in their 40s.

Why are older men at elevated risk?

The most prominent hypothesis is that the sperm of older men has **accumulated many spontaneous mutations** that the men pass along to their children.

Sperm divide more often than egg cells do. With each division, a cell's DNA is copied, presenting an opportunity for mutations to occur. One analysis of families in Iceland showed that with each passing year, a man transmits an **average of two more** spontaneous, or de novo, mutations to his child.

Studies in mice confirm that pups of older male mice harbor a relatively large number of mutations. And this hypothesis is consistent with the observation that a child with autism who has an older father tends to be the only child with autism in that family.

Other factors must contribute as well, however. A mathematical model of autism inheritance indicates that de novo mutations account for **no more than 20 percent** of the increased risk of autism among children of older fathers.

What else could explain these patterns?

It is possible that the connection runs the other way: Men who are likely to father a child with autism may have children relatively late in life. These men may have autism traits that delay their ability to find a partner.

Changes in **chemical tags on sperm DNA** as men age could also play a role. This hypothesis is consistent with epidemiological studies showing that the **age of a grandparent** at the time of a parent's birth can **affect a grandchild's autism risk**, and age alters chemical tags on sperm in mice. But this idea is controversial: There is no direct evidence that these tags are transmitted across generations in people.

Studies have noted additional factors, including an elevated risk of autoimmune disease in older parents. And because they are likely to be **relatively wealthy** compared with younger parents, older parents may be more likely to seek an evaluation for their child.

How does a mother's age influence risk?

A woman's chance of having a child with autism also increases steadily with age. But several studies have found that **teenage mothers** are also at **increased risk**. Overall, researchers have conducted fewer studies of **maternal age and autism**, and the results are not as clear-cut as they are for fathers. The effects of maternal age are more difficult to detect in epidemiological studies because women have children over a narrower age range than do men.

The number of de novo mutations in egg cells increases with age, although to a lesser degree than it does in sperm. As with men, women who have autism traits may have children late.

Does the trend toward having children later in life explain the increase in autism prevalence?

Probably not. Independent calculations suggest that the **trend toward later parenthood** accounts for only about 1 to 5 percent of the **increase in autism prevalence**. But investigating the link between parental age and autism risk could provide clues to the biology underlying the condition.