NEWS

The link between parental age and autism, explained

BY **SARAH DEWEERDT**

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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 increased odds of having a child with autism 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 have elevated odds 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.

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 do the odds of fathering a child with autism 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 odds increase steadily over time rather than suddenly rising after a certain age.

How big is the increase?
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 odds of autism among children born to fathers older than 45 are about **75 percent higher** than 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 chance 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 do older men have higher odds of fathering children with autism?
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 study in Iceland showed that spontaneous, or de novo, mutations accumulate more rapidly in men than in women. Another study in the same country suggested that with each passing year, a man transmits an **average of two more** of these 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. Mathematical models of autism inheritance have indicated that de novo mutations account for **about 20 percent** of the increased odds 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 odds of having autism**, 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 elevated odds of autoimmune conditions 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 the odds of having a child with autism?
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.

Some studies have suggested that a woman's chance of having a child with autism also increases steadily with age. 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. However, a comprehensive analysis found that for a woman over age 35, the chance of having a child with autism is **lower than for younger women**.

That study also suggested that women under age 25 are more likely to have a child with autism than older women. The finding echoed that of several other studies that reported that **teenage mothers** also have **increased odds** of having a child with autism.

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 could provide clues to the biology underlying the condition.

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