

The Link Between a Mother's Lupus and a Child's Autism

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At the turn of the 21st century, the prevalence of autism spectrum disorder among American children was roughly 1 in 150. That's [according](#) to data collected by the Autism and Developmental Disabilities Monitoring Network of the U.S. Centers for Disease Control and Prevention. A decade later, in 2010, the prevalence had risen to 1 in 68 children. By 2020, it had climbed again—to 1 in 36 children. "The prevalence of Autism Spectrum Disorder (ASD) has increased dramatically in recent decades, supporting the claim of an autism epidemic," wrote the authors of [a 2020 study](#) in the journal *Brain Sciences*.

The precise cause and extent of that epidemic are contested. Some researchers [have observed](#) that the diagnostic criteria for ASD have evolved during that time—stretching and broadening to include a wider array of conditions. And so part of the rise in diagnoses, they argue, is likely attributable to dilating conceptions and a deeper understanding of autism. Still, the increasing prevalence of ASD diagnoses has spurred greater scientific interest in the underlying causes of the disorder. That work has revealed a possible connection between ASD and autoimmune conditions, including systemic lupus erythematosus (SLE).

“For quite a while, there’s been a link between maternal autoimmune diseases and risk for having a child with autism,” says Paul Ashwood, a professor of medical microbiology and immunology at the University of California, Davis and the [MIND Institute](#), which focuses on autism and other neurodevelopmental conditions. He mentions work based on nationwide data collected over a period of many years from mothers and their offspring in Denmark. That [research](#) found that prenatal exposure to a number of different maternal autoimmune diseases, including both lupus and rheumatoid arthritis, was associated with an increased risk for an eventual autism diagnosis.

Since then, more research has firmed up the apparent association, and also found evidence of a broader connection between a pregnant woman’s immune system and the risk of an offspring with autism. “What we’ve been looking at a lot more recently is how anything that generates a maternal immune response could be linked to autism risk,” Ashwood says.

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Antibodies and the developing brain

In response to a threat, such as a virus or other pathogen, the immune system produces protein antibodies that are intended to neutralize or

eliminate the danger. But among people with autoimmune conditions such as systemic lupus erythematosus, the immune system produces antibodies that attack the body's own healthy proteins or tissues. These are called autoantibodies.

In [a 2015 study](#) in the journal *Arthritis and Rheumatology*, a group of Canadian researchers found that children born to women with systemic lupus erythematosus were nearly twice as likely to develop autism as children of women who did not have SLE. Furthermore, the children of mothers with SLE tended to be diagnosed with autism at a younger age than those of mothers without SLE.

"In-utero exposures to maternal antibodies and cytokines [proteins that regulate the growth of immune system cells] are important risk factors for ASD," the authors of that study wrote. Women with SLE "display high levels of autoantibodies and cytokines," which have been shown in animal models to alter fetal brain development and induce behavioral anomalies in offspring, they added.

"Maternal antibodies, including autoantibodies, start crossing the placenta barrier around day 100 of gestation, and we know that this can affect the developing fetus," says [Judy Van de Water](#), professor of medicine and associate director of biological sciences at the University of California, Davis and the [MIND Institute](#). "One of the things we're looking at is how these autoantibodies or other aspects of the mother's immune response could affect neurodevelopment."

Some [research](#) has already found that maternal autoantibodies related to SLE may lead to the development of heart conditions and also blood and liver abnormalities in a developing fetus. Van de Water and her colleagues are examining whether and how other autoantibodies may similarly affect fetal brain development. "Several of the proteins that these autoantibodies target are really highly expressed in the developing brain, and not the mature brain," she says. This may create unique exposure risks for a

developing fetus.

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The immune-autism link

Apart from lupus, [several other](#) maternal autoimmune disorders, including [rheumatoid arthritis](#), have been tied to an increased risk for having children with autism. The same is true of immune-related conditions such as asthma and allergies. Van de Water and other researchers are now taking a broad look at how a pregnant woman's immune system activity may affect the fetal brain. "Anything that impacts maternal immune homeostasis or the balance of the immune response in the mother could impact neurodevelopment in the child," she says. "So we're looking at different immune systems responses—what the response is, how intense the response is, the makeup of inflammatory markers—and their relationships to autism."

An autoimmune condition like lupus is one source of a heightened maternal immune response, but Van de Water says that, under the right conditions, just about anything that triggers an immune reaction could potentially affect neurodevelopment in ways that contribute to autism. "We're looking at a lot of different maternal immune activations or perturbations—whether from an existing condition or illness, or something that happens during pregnancy," she says.

In particular, experts highlight the role that inflammatory cytokines may play in autism risk. "The way to think about cytokines in the fetal environment is that they can potentially act in a dose response manner—just as too much is bad, then too little is also bad, but there is this goldilocks level that you need to have for appropriate growth," Ashwood says. "If there's some kind of immune condition or inflammatory response that leads to the constant production and release of these cytokines, those could cross the placental

barrier and affect fetal development."

In the brain, for example, the presence of cytokines "could affect neuron growth, neuron proliferation, the connection of neurons to other neurons, synapse formation, neuronal migration, and all sorts of processes that are necessary to build an interconnected network as the brain grows," he explains. "Having those systems slightly off-kilter can potentially affect the trajectory of neurodevelopment."

Lupus and other autoimmune disorders are one potential source of cytokine imbalance. But Van de Water says that obesity is another inflammation-related condition—and a far more common one than lupus—that could produce the sort of immune activity that contributes to autism. "Obesity has a major inflammatory component attached to it," she says. "We just published [a paper](#) looking at this, and it turns out that the biggest maternal risk factor for autism was not any autoimmune disease, but asthma and allergies coupled with obesity. You put these two together with obesity and the risk was significantly greater."

Another potential connection between a mother's immune activity and her offspring's autism risk is the microbiome—the community of bacteria that inhabit the gut. [Some research has found](#) that the metabolites produced by a mother's gut bacteria can affect the neurodevelopment of the fetus. Furthermore, [there's evidence](#) that infections, metabolic stress (such as obesity), and other immune-related events can lead to maternal microbiome imbalances that, potentially, could raise her offspring's risk for autism.

On top of this, [there's evidence](#) that people with autism share some distinct microbiome characteristics, and that gut-related symptoms—diarrhea, constipation, and abdominal pain in particular—are [common comorbidities](#) among people with autism. "There's a lot of interest right now in the microbiome—how it's formed, the way it nourishes the body, and how it shapes the activity of the immune system," Ashwood says. There's also

been much recent interest in the so-called “gut-brain connection,” and [science has established](#) that the gut’s microbiota influence brain connectivity and functioning.

It’s not certain yet, but it’s possible that maternal autoimmune disorders and other immune-related perturbations could directly or indirectly affect the microbiome of the fetus in ways that contribute to the development of autism.

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A multifaceted disease

While there are several plausible mechanisms that could tie autoimmune disorders to autism, experts say this is likely only one small part of the autism equation. “It’s worth remembering that autoimmunity in the general populace is pretty low,” Ashwood says. Also, [research](#) on the link between maternal lupus and autism has found that while the risks are elevated, women with the autoimmune condition were still at low overall risk for having a child with autism.

Apart from maternal immune conditions, there’s growing [evidence](#) of the role that genetics play in a person’s risk for autism. “More than 100 genes are known to confer risk, and 1,000 or more may ultimately be identified,” wrote David Amaral, a distinguished professor at the University of California, Davis and the MIND Institute, in [a 2017 paper](#) on the causes of autism. He goes on to explain that, most likely, a mix of genetic and environmental factors contribute to the development of autism. “It seems clear at this point,” he writes, “that when all is said and done, we will find that autism has multiple causes that occur in diverse combinations.”

Van de Water likewise emphasizes this point. Autism spectrum disorder is a diverse and multifaceted condition, and its underlying causes are likely equally complex. Lupus and other immune-related conditions may be a

piece of the puzzle, but they're just one of many. "Anyone who tells you they know the cause of autism doesn't know autism very well. There are many layers to it," Van de Water says. "There seems to be a relationship between the mother's immune activity and autism, but we don't have all the answers yet."