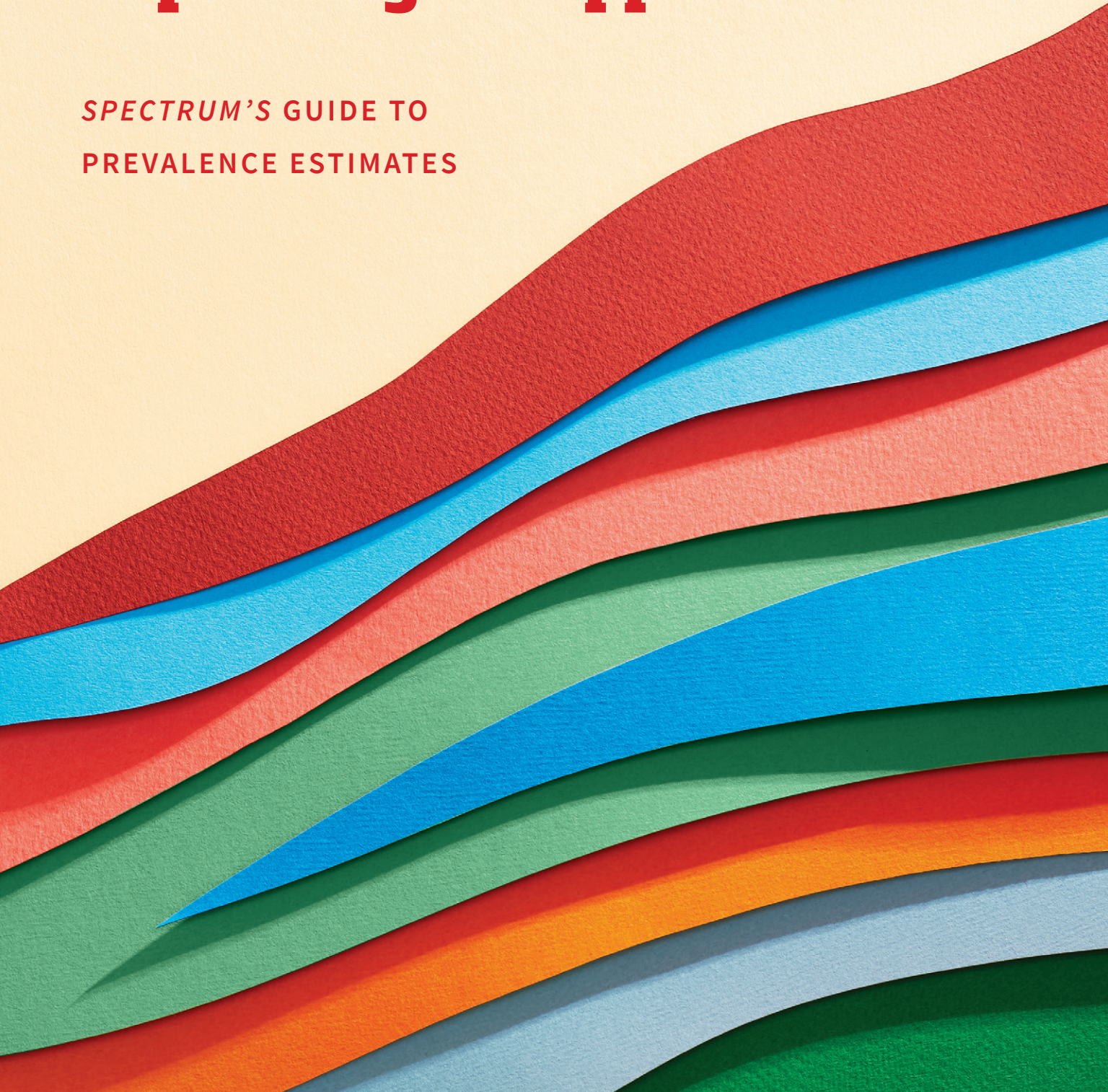
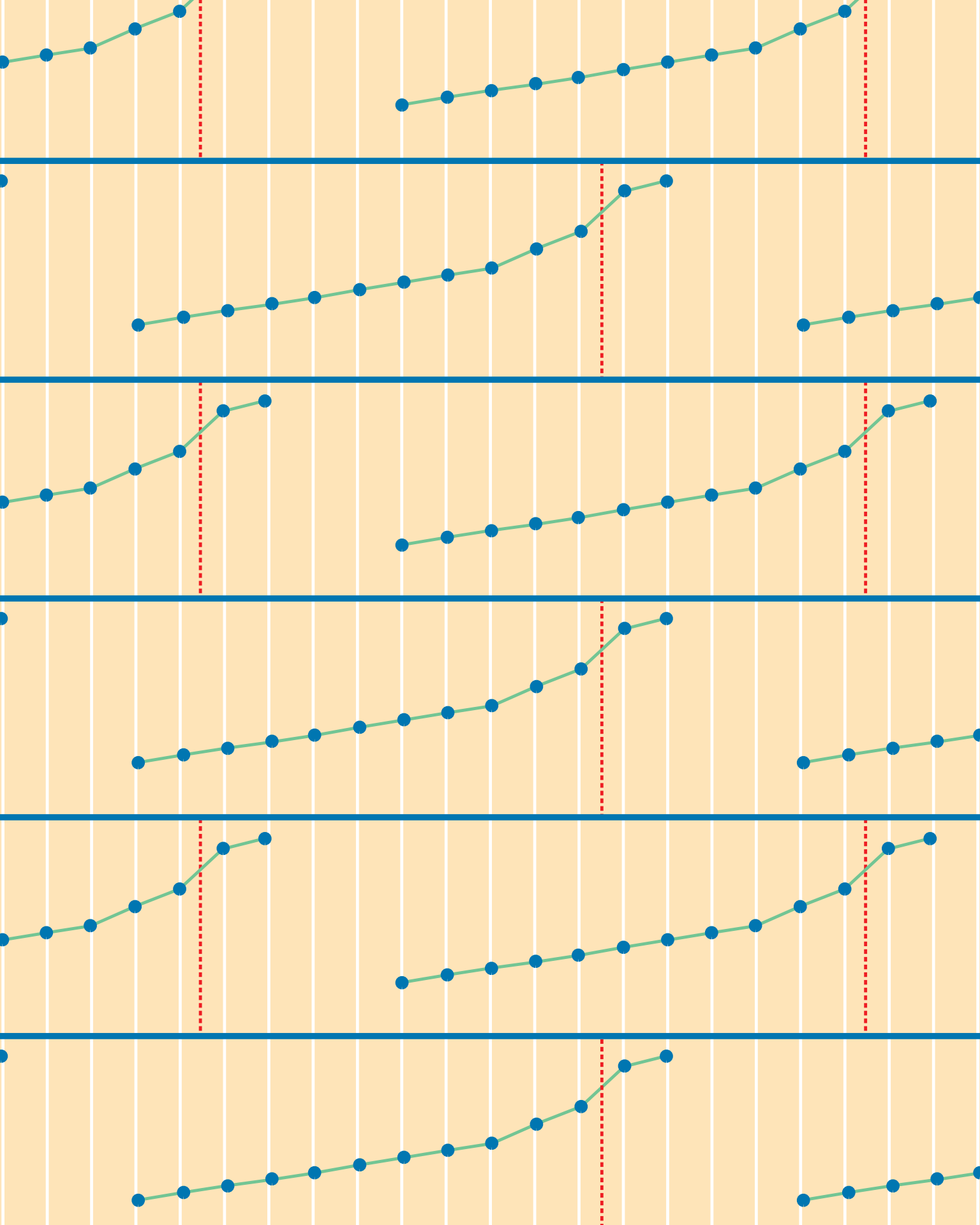


# **Autism by the Numbers: Explaining its Apparent Rise**

*SPECTRUM'S* GUIDE TO  
PREVALENCE ESTIMATES





# **Autism by the Numbers: Explaining its Apparent Rise**

*Spectrum's* guide to prevalence estimates

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**Spectrum** has covered innumerable twists and turns in researchers' efforts to unravel the mysteries of autism. Among the many puzzling aspects of the condition, one of the most vexing has been the surprisingly rapid, persistent and global rise in its prevalence. As surveys and epidemiological studies around the world have made clear, life on the spectrum is far more common than most societies previously realized.

But questions abound. How common, exactly? Is autism really far more prevalent among children today than in generations past? Among the many factors that could each account for part of the observed rise, which are most important?

We created this book—our fourth annual compendium since 2018—as a guide to help readers think about these complex questions. The book opens with a special in-depth exploration, published here for the first time as Part 1, that walks us systematically around the global phenomenon of increasing autism prevalence, stopping at several vantage points to examine possible explanations. What might be changing developing brains in ways that make autism more common? What societal shifts are making autism more widely recognized? What subtleties of scientific methodology play important roles in the phenomenon? And which studies offer clues to where the rising curve of autism prevalence may eventually plateau?

The story is punctuated by relevant articles from *Spectrum's* archive, and Parts 2 through 5 of the book are then organized along parallel lines to present more of our recently published coverage. Though the scientific search for definitive answers to these important questions continues, we hope that you will find in this guide new and useful ways of making sense of the numbers, trends and hypotheses about autism prevalence.

— *The Spectrum team*

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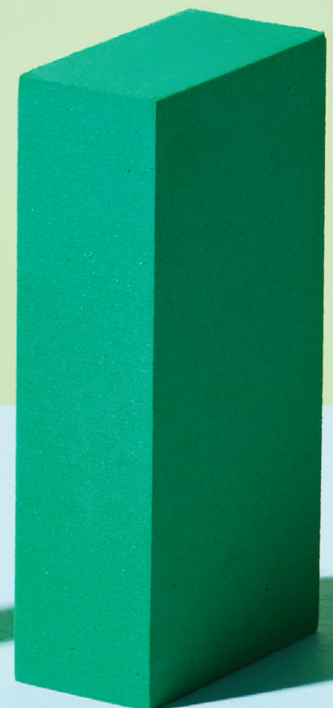
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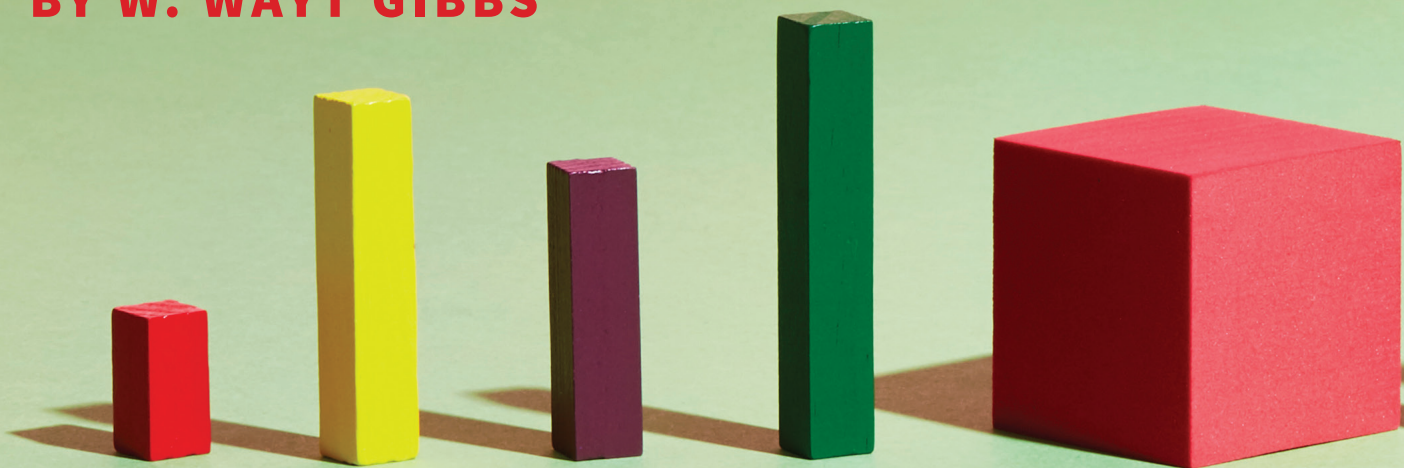
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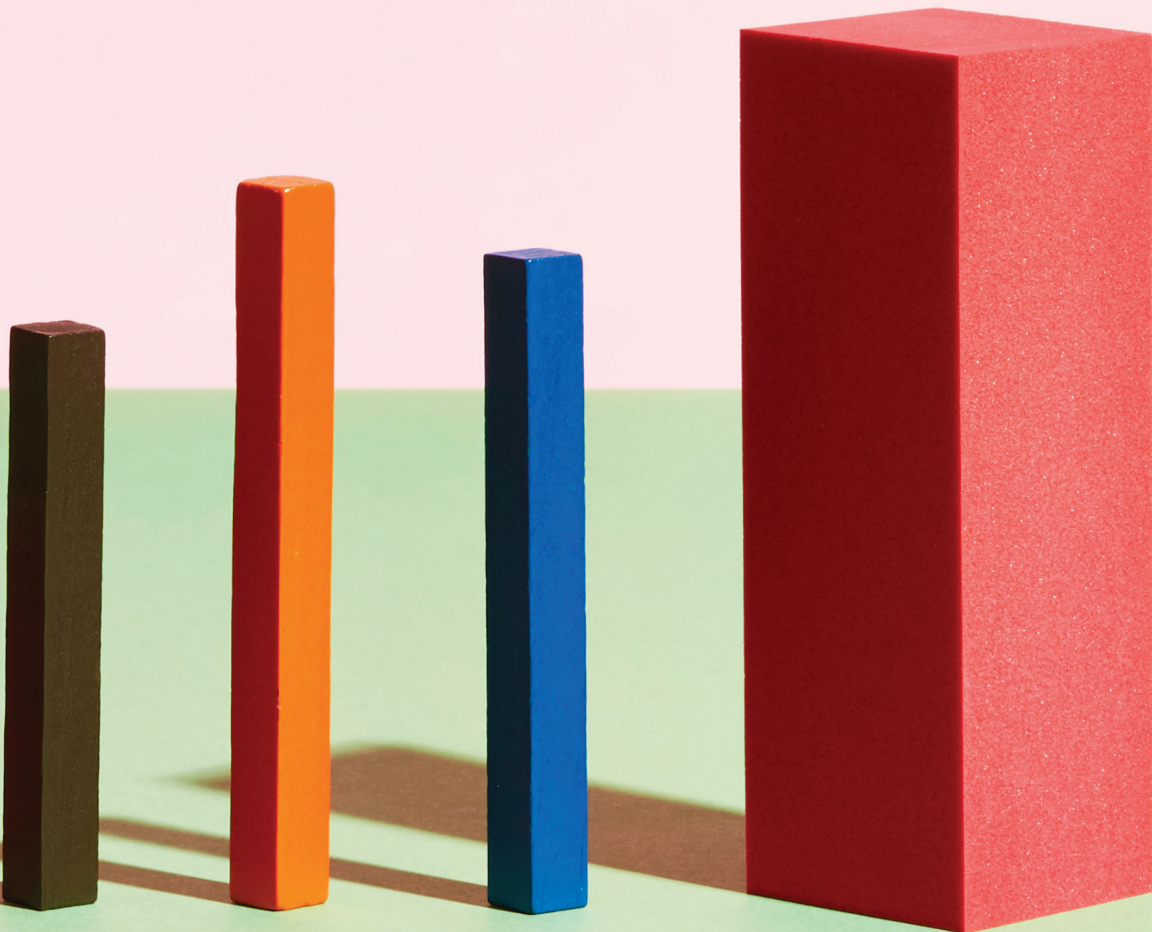
## An 'Epidemic' of Uncertain Proportions

BY W. WAYT GIBBS





*We're seeing more  
autism than ever  
before. It's important  
to understand why—  
and why the increasing  
prevalence numbers matter.*



# 1

## Brick Township

*After a housewife rallied parents to find out why her children and so many others in their small town had autism, the CDC launched an investigation. What it found shook researchers' long-held belief that autism is rare.*

In September 1997, Bobbie and Bill Gallagher of Brick Township, New Jersey, sat down with their congressman to ask for help investigating what looked to them like an outbreak of autism. Two of their three children had been diagnosed with the condition, despite no family history. “We started going to a parent support group,” Bobbie recalls, where she was surprised to discover how many other local parents had 2- and 3-year-old children on the spectrum.

“So I made a flyer asking families to send information back if their child was born here [and] if they had autism,” she says. “One mom put it in all the backpacks of the kids on her son’s school bus.”

About 45 flyers came back—many more than she had expected from a quick informal survey of this beach town of 75,000 people, about 50 miles north of Atlantic City. “It just felt like it wasn’t a coincidence anymore,” she recalls. “There was something that was happening.”

The trauma that parents had endured one town over, in the village that became Toms River, was on Gallagher’s mind. Years of toxic waste dumped by industrial plants had been linked there to an epidemic of childhood cancers in the mid-1990s. She wondered: Could something in the water, air or soil in Brick Township be making autism more common in her community?

Chris Smith, her congressional representative, asked the Centers for Disease Control and Prevention (CDC) to investigate. The CDC and the Agency for Toxic Substances and Disease Registry quickly sent in a team of about 20 researchers and other personnel. The scientists pulled records from the town’s schools and doctors’ offices.

They collected lists of autistic children from parent-support groups—and more names from parents who had seen news stories about the study and called in with concerns. A child psychologist and a neurodevelopmental pediatrician conducted a comprehensive clinical assessment of each child identified as possibly autistic.

In January 1999, one of the lead investigators and two other officials sat down with the Gallaghers in their living room to explain what they had found. Bobbie struggled to follow their technical language. “I was a housewife; Billy was a fisherman,” she says. But she remembers them saying that more than 1 in 90 young children in Brick—more than 1 percent—might have autism.

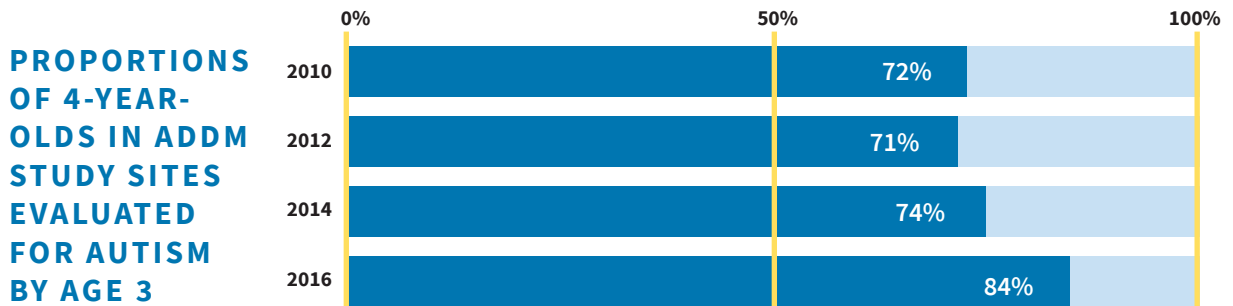
“I was shocked by that number,” she says. At the time, many experts believed that autism was rare, affecting fewer than 1 in 2,500—around 0.03 to 0.04 percent of school-age children in the United States.

At seven o’clock the next evening, residents gathered at the Brick library to learn what the CDC had found. The agency provided copies of the technical report and tacked printouts of key charts and tables to a wall. CDC experts were there to answer questions in one-on-one conversations. But Gallagher says that she and her neighbors largely milled

## Looking harder for autism, and finding it

*In its 2020 report on autism, the CDC observed that children were being screened for autism more widely than before, yielding earlier diagnoses.*

After holding mostly constant for several years, the fraction of 4-year-olds assessed for autism rose in 2016, according to data collected by the U.S. Centers for Disease Control and Prevention through its Autism Developmental Disabilities Monitoring Network (ADDM). That increase suggests that caregivers and health professionals have started spotting and referring autistic children earlier in life.



about waiting for an explanation in plain English that never came.

“Eight o’clock came along; they packed their bags,” she says. “They left, not to be heard from or seen again.” She says follow-up phone messages she left with the agency were never returned, leaving her bewildered as to why the researchers had not followed up on possible environmental causes. “I was expecting somebody to come into my home and test my water, test my soil, test my blood,” she says, as had been done in Toms River.

Two years later, the CDC group published a paper in the journal *Pediatrics* reporting that 60 children in Brick Township met then-standard criteria for autism in 1998, out of an estimated population of 8,896 boys and girls age 3 to 10 years. That ratio works out to a prevalence of 0.67 percent, or about 1 case of autism in every 148 children.

Because the researchers examined only a subset of children in Brick—those who doctors, parents or teachers had already identified as possibly having autism—the estimate came with error bars. Among 3- to 5-year-olds, the paper reported, the prevalence probably fell within the range of 0.51 percent to 1.13 percent, or from 1 in 196 to 1 in 88. It may have been that last number that stuck in Gallagher’s memory.

These numbers, 16 to 26 times higher than previously measured in the U.S., caught the attention of researchers as well as autism advocates. It was a watershed moment: “a hint that it’s not a rare disorder,” says Andy Shih, senior vice president of public health and inclusion at Autism Speaks.

The CDC’s findings—along with other prevalence estimates of 0.31 to 0.60 percent from similar studies in the 1990s of small European towns—raised some troubling questions: Had autism really spiked in the U.S. by more than tenfold? Might pollutants in certain areas be steering the development of children onto the spectrum? Had pediatricians and public health officials been overlooking most of the autism in the communities they served?

We had no way to tell, wrote epidemiologist Eric Fombonne, in [a commentary](#) for *Pediatrics* in 2001. Fombonne had overseen the first large-scale study of autism prevalence in France in the 1980s and then moved to London to work with the famous child psychiatrist Michael Rutter to develop new diagnostic criteria for autism and other child psychiatric disorders. Under the provocative title “Is

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<https://pediatrics.aapublications.org/content/107/2/411>

there an epidemic of autism?” Fombonne warned that the picture was muddled by poor research practices, shifting diagnostic criteria and problems with how records were being kept and analyzed.

“We simply lack good data to test hypotheses on secular changes in the incidence of autism,” he wrote at the time. Epidemiologists couldn’t rule out a real, persistent increase in the fraction of children whose brains showed autism characteristics. But they would have to build more sophisticated monitoring systems to measure the true depth and breadth of any such trend, he argued.

Many of the improvements Fombonne wished for 20 years ago are still on autism researchers’ wish lists today. But the fog of confusion has begun to lift. Surveillance systems, while still imperfect, have multiplied and improved. Extensive debate within the field has produced a broad consensus that changes in how autism is defined and diagnosed can account for much—though perhaps not all—of the increase in measured prevalence. The apparent epidemic in autism, in other words, is mostly a sociological phenomenon rather than a neurological one.

And yet there could be changes in the air we breathe, the water, food or medicines we consume, the choices that parents and doctors make during pregnancy and childbirth that have been nudging human development toward autism slightly more frequently than before. Tantalizing evidence—not yet conclusive—links several biological influences to small increases in the fraction of children each year who exhibit behavior on the spectrum, however that is defined.

Then there is a third, subtler set of factors at work: the methodological ones. These have to do with the behavior of the scientists who generate autism prevalence estimates, such as the oft-quoted but misleading statistic that **1 in 54 children** in the U.S. had autism in 2016. A lot of statistical sophistication goes into calculating those numbers. There is no one right way to do it, but there are a lot of wrong ways. The assumptions that researchers make and the way they treat unknowns and uncertainty can bias or distort the prevalence estimates that appear in their papers.

Before we dive into the various factors that may explain the sharp rise in autism prevalence, it’s important to know how it has

*The CDC’s findings raised some troubling questions: Had autism really spiked in the U.S. by more than tenfold? Had pediatricians and public health officials been overlooking most of the autism in the communities they served?*

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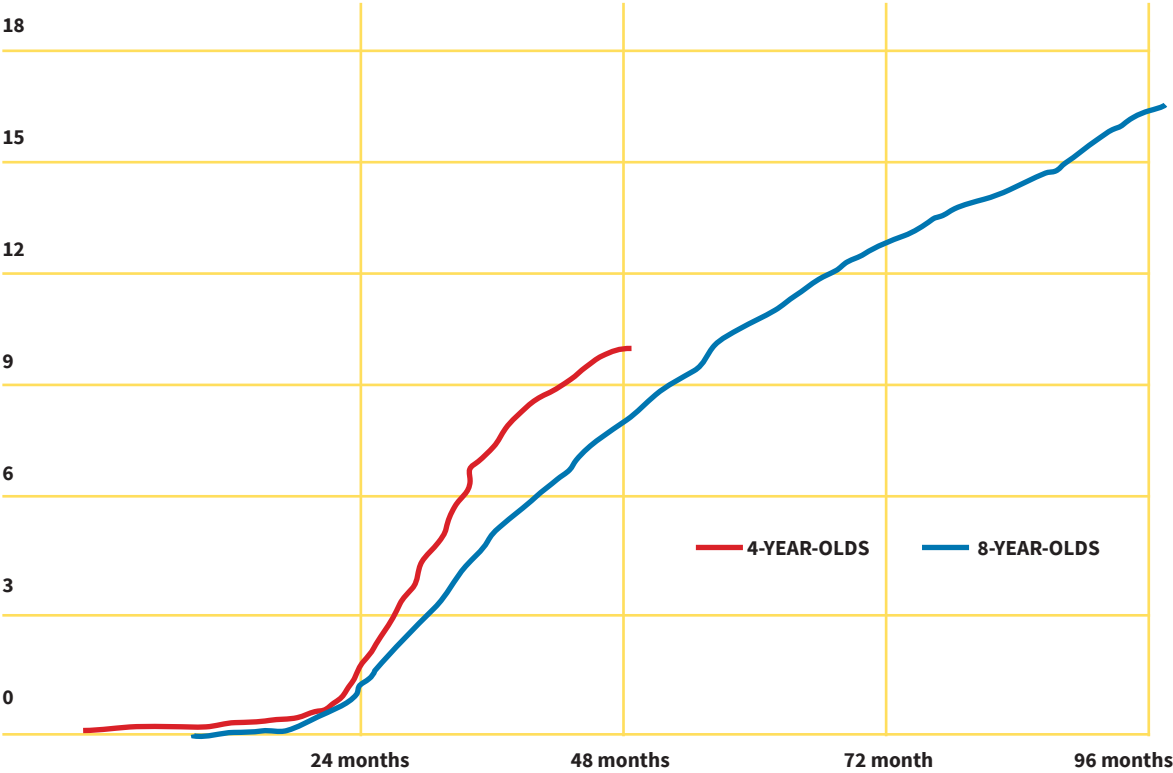
<https://www.spectrumnews.org/news/new-u-s-data-show-similar-autism-prevalence-among-racial-groups/>

been measured, particularly in the U.S. The process is not nearly as straightforward as many people think.

Against that backdrop, we'll then take a tour through each of the plausible explanations in turn: first the biological factors, then the sociological and methodological ones. After that, we can look closely at four recent studies that have used innovative or especially rigorous methods. These studies shed new light on the rising prevalence curve and suggest when it might level off. They also raise deeper questions of whether it is even possible to measure the true prevalence of autism, and whether, at some point, it might make sense to give up on that goal.

### CUMULATIVE AUTISM PREVALENCE IN 2020, BY AGE AT TIME OF DIAGNOSIS

These curves from the 2020 ADDM report show that the measured prevalence of autism (represented in cases per 1,000) by age among children in the study rose faster for those born in 2016 (red curve) than it did for those born in 2012 (blue curve). Again, this pattern suggests that autistic children are being identified at younger ages than before.



# Laying Hands on the Elephant

# 2

*Knowing how fast autism might be growing is difficult.  
Step one: measure it consistently.*

In March 1998, just six months after the Gallaghers approached their Congressional representative for help, the Princeton-based National Alliance for Autism Research proposed setting up five centers around the country to study the prevalence and causes of autism. That idea took root and grew into the CDC's Autism and Developmental Disabilities Monitoring (ADDM) Network, a smattering of research teams throughout the U.S. that estimate, every two years, the prevalence of autism among some or all of the 4- and 8-year-old children in their area.

To do this, the scientists collect autism-related notes and diagnoses from the children's medical and educational records. The researchers then try to infer from those which children likely have autism.

Maureen Durkin, an autism epidemiologist at the University of Wisconsin-Madison who has worked with the CDC on autism surveillance since 2003, points out that “those data are collected under public health authority,” similar to the way that counties tally up COVID-19 test results. Parents aren't asked for permission to look at their children's records. As a consequence, Durkin says, “we can't really contact anybody—see, that's the problem,” along with the high costs of individual evaluations, that prevents ADDM teams from examining the children themselves.

Fombonne and others say that the reliance on inferred diagnosis

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[https://stacks.cdc.gov/  
view/cdc/6844](https://stacks.cdc.gov/view/cdc/6844)

rather than clinical exams raises concerns about overdiagnosis in the ADDM numbers. We'll come back to that criticism later.

It took the CDC nearly a decade—until 2007—to publish *its first estimate* of 0.67 percent, which was based on data collected in 2000 from six study sites. The network then grew, and the ADDM now includes 11 sites, stretching from New Jersey to Arizona.

Reporters and scientists commonly cite the ADDM's 'overall' prevalence figure—an unweighted average of prevalence estimates for each of the 11 sites. When the CDC announced its most recent statistics in March 2020, for example, the headline prevalence among 8-year-olds was 1.85 percent. Journalists, activists and researchers expressed that number in various equivalent ways. Some cited the ratio as 185 per 10,000 children, for example, or—dividing the denominator by the numerator—as 1 in 54.

To keep things simple, I'll stick with percentages and rounder numbers. Reporting more than two significant digits gives a false sense of precision because the margins of error on these estimates—usually given in the form of a '95 percent confidence interval' or CI—are often quite large. Humans in the real world are hard to measure. The statistical methods of epidemiology frequently can do no better than say that you can have 95 percent confidence that the true value of whatever your study actually measures—and many studies are designed to measure something other than the true value of autism prevalence—falls within that interval. Then again, there is a 5 percent likelihood that it doesn't. As a general rule, smaller studies produce wider brackets, though factors other than the number of participants also come into play.

In fact, studies of autism prevalence vary so greatly in size and design that those intervals matter a lot. So from here on out, not only will I convert prevalence estimates to percentages, but I will also tell you the span of that 95 percent CI. Let's start with that 1.9 percent figure the CDC released in March 2020: Actually, the estimate was from 1.8 to 1.9 percent.

There is something very curious about that impressively narrow confidence interval, Fombonne hastened to point out when I sat down with him in 2019 in his modest office in a refurbished nurses' dormitory on the Portland campus of Oregon Health and Science

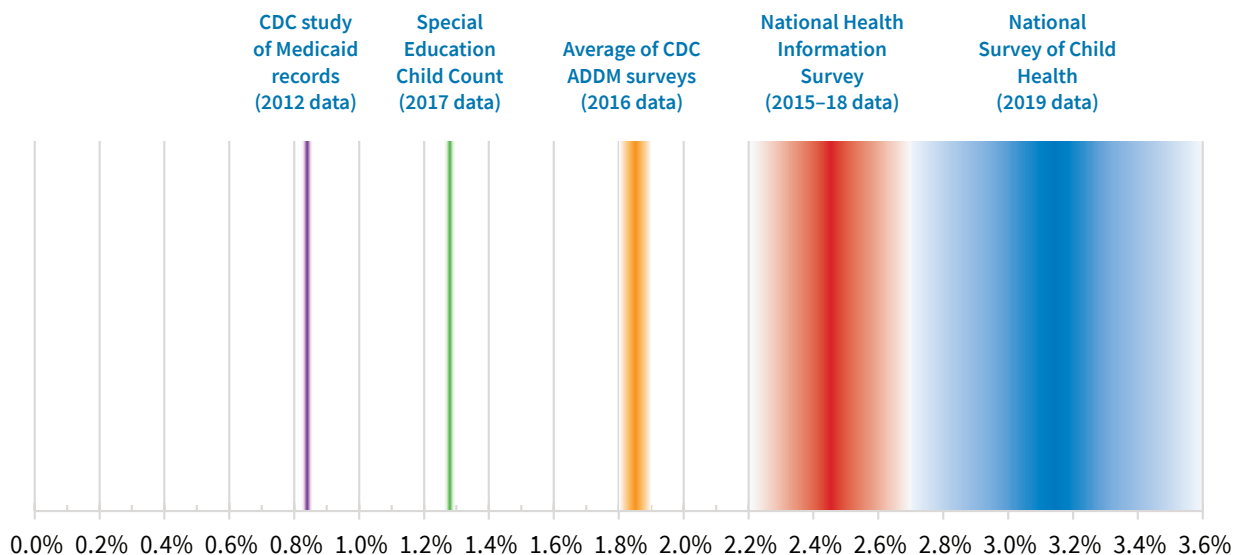


# How common is autism in the United States?

## The answer depends on which agency you ask.

*Federal agencies have put out five sets of numbers. For some years, none of the estimates are compatible with the others.*

More autism prevalence studies have been performed in the United States than in just about any other nation, yet a definitive answer remains elusive. Several arms of the federal government have tried to measure the extent of childhood autism in the country, and they have tried a variety of techniques ranging from parent surveys to Medicaid records. Some of the estimates, such as one derived from the National Survey of Child Health, report 95 percent confidence intervals around their central estimates, which we show below as fuzzy regions. Other agencies just put out a single number. It may seem remarkable how far apart these measurements are. In part, that's because some of the numbers are old, and others have been recently updated. But mainly the disparities reflect the fact that counting young people who have autism is a surprisingly hard thing to do accurately.



Source	Low CI	Median	High CI	Estimate for year(s)
HRSA National Survey of Child Health	2.70%	3.10%	3.60%	2019
NCHS National Health Information Survey	2.20%	2.50%	2.70%	2015-2018
Dept of Education Special Education Child Count		1.27%		2017
CDC ADDM	1.80%	1.85%	1.90%	2016
CDC Medicaid study	0.82%	0.82%	0.83%	2012

University. The prevalence numbers calculated for each of the 11 ADDM sites vary so much that only two of them fall within the margin of error for that overall, 1.9 percent estimate that has already been cited hundreds of times. For the other nine ADDM

none for the U.S. as a whole fit within the confidence intervals of the others.

Like the ancient parable about a group of people in the dark trying to describe an elephant by touch alone, the scientists who describe the dimensions of

# **We have five periodic measurements, five clues, but still no definitive answer to what we really want to know: How heavy is this elephant, and how fast might it be growing?**

sites—where measured prevalence ranged from 1.2 to 1.4 percent around Denver, Colorado up to 3.0 to 3.3 percent in four counties in New Jersey (including Brick Township)—the numbers are statistically incompatible with the overall estimate and, in many cases, with each other.

Here's another curious wrinkle: The ADDM estimates are just one of five sets of autism prevalence numbers the U.S. government publishes. Four originate from the Department of Health and Human Services, and the fifth from the Department of Education. All five are different, and in some years

autism give accounts that vary dramatically depending on how they take its measure—and also when, because this particular elephant may be growing.

When the CDC filtered insurance claims for 26 million Medicaid participants to identify children who had autism-related treatment codes, for example, it was grabbing the tail of the elephant; that view saw autism in just 0.82 to 0.83 percent of children age 3 to 17 in 2012—the most recent year on record for that estimate.

The Special Education Child Count, performed by the Department of Education, seizes a tusk. It

uses criteria that vary from state to state to tally children age 6 to 17 receiving autism services in 47 U.S. states. The result: a prevalence estimate for 2017 of 1.3 percent, with a tight confidence interval. The ADDM's latest national estimate of 1.8 to 1.9 percent, by comparison, looks more like an elephant's trunk.

And then there are the two national surveys. Although the ADDM studies are often casually discussed as describing autism among all children nationwide, that interpretation is incorrect. The ADDM sites are geographically concentrated, and they do not reflect the racial and ethnic composition of the U.S. population.

But over at the U.S. Health Resources and Services Administration (HRSA), an imposing 15-story glass and steel building in Rockville, Maryland—which I also visited in 2019—epidemiologist Michael Kogan and his team do try to come up with valid national estimates. Their periodic National Survey of Child Health (NSCH) analyzes responses to questionnaires distributed to a nationally representative group of tens of thousands of parents. The questionnaire asks about their children's health, including whether any of their children have ever been diagnosed with autism and whether they currently have the condition. Based on the survey for 2019, the HRSA put the prevalence of autism for age 3 to 17 in the U.S. at 2.7 to 3.6 percent. There's the leg of the giant.

Estimates that high—1 in 83 girls and 1 in 20 boys on the spectrum—have raised a lot of eyebrows.

But corroboration of a sort came in data from a different nationally representative poll of parents. In 2020, CDC and HRSA researchers, drawing on results from the National Health Information Survey (NHIS), estimated the prevalence of autism among U.S. children from 2015 to 2018 as 2.2 to 2.7 percent. Another leg, it seems.

So we have five periodic measurements, five clues, but still no definitive answer to what we really want to know: How heavy is this elephant, and how fast is it growing? No one has yet invented the equivalent of a scale: an objective, 100 percent reproducible test for autism on which all children could be evaluated several times throughout development. Fombonne, who has overseen and participated in autism prevalence studies all over the globe, says he's skeptical that such a screening test will ever be practical.

But size and growth are distinct questions. Even absent any single, reliable point measurement of how prevalent autism is in a large population, the persistent upward trend across many measures demands explanation. Society needs to prepare for the increasing costs that autism adds to health care, education and social assistance budgets. Those expenses could approach \$1 trillion a year in the U.S. alone if prevalence in the population at large stabilizes around 1.5 percent, according to a 2015 projection by two economists. Prevalence must plateau eventually, but when?

# POSSIBLE PAYOFFS FROM EARLY INTERVENTIONS

BY JESSICA WRIGHT

*The United States already spends more on autism than it does on most other chronic health conditions. But investment in early interventions could pay off down the road.*

Autism cost the U.S. \$268 billion in 2015—roughly 1.5 percent of the country’s gross domestic product<sup>1</sup>. By 2025, the price tag could balloon to \$461 billion.

These estimates, published in the *Journal of Autism and Developmental Disorders*, were the first to forecast the costs of autism a decade into the future. They assume an autism prevalence of 1.1 percent and that 40 percent of people with autism have intellectual disability, one indicator of autism severity.

“Autism is very expensive for the entire economy and, in general, for society,” says lead researcher J. Paul Leigh, professor of health economics at the University of California, Davis. “It’s more expensive than I think most people realize.”

The ‘cost’ of autism for 2015 is roughly on par with a 2012 estimate for diabetes and more than five times that of stroke or hypertension in 2010. If autism’s expense rises as predicted, it will quickly surpass that of diabetes, considered one of the country’s biggest public health problems, says Leigh.

The exact size of the bill is less important than knowing that the rising costs are unsustainable, says David Mandell, associate professor of psychiatry and pediatrics at the University of Pennsylvania. “What we need now is to ask, ‘What are we going to do about it?’”

## AVERTING CRISIS:

In a 2014 study, Mandell and his colleagues found that the lifetime cost of autism for one individual is \$1.4 million.

That number jumps to \$2.4 million for a person who also has intellectual disability<sup>2</sup>.

The new study builds off those estimates, calculating total societal costs for 2015 and 2025 using population estimates from the 2012 national census, and adjusting for inflation in medical costs and productivity.

The costs span several categories: special education, medical services, non-medical services such as after-school programs, loss of productivity (of parents and individuals with autism) and residential care.

Some of these costs are “good”—that is, designed to help affected individuals, says Martin Knapp, professor of social policy at the London School of Economics and Political Science, who was not involved in the new study. “Bad” costs, by contrast, are consequences of poor support—for example, a parent having to leave work to care for her child.

“We need to spend the money so that it’s more focused on evidence-based interventions and less focused on crisis,” Knapp says.

Because costs vary across a lifetime, the studies break them down by age: 5 years and under, 6 to 17 years, and adults. They also separate individuals with autism who have intellectual disability from those who don’t. The former often have a higher need for services.

Intellectual disability is, however, a crude way to account for the wide range in abilities across people with autism, says Maureen Durkin, professor of population health sciences and pediatrics at the University of Wisconsin-Madison.

“If we actually knew what percentage of people with autism are able to work and the impact of autism on someone’s family income, that would help narrow this a lot better,” she says. “It just shows how little we know about costs.”

## LOOKING AHEAD:

For 2025, the authors applied the same 1.1 prevalence rate to a population projection for that year. But assuming a stable rate of 1.1 percent for all individuals with autism may result in a conservative estimate.

The latest report from the U.S. Centers for Disease Con-

trol and Prevention finds that 1.47 percent of 8-year-old children have autism. Extrapolating this rate to all people with autism puts costs at roughly \$358 billion in 2015 and \$616 billion in 2025. Assuming that autism rates will continue to climb as they have over the past few years lifts the 2025 estimate to more than \$1 trillion.

But the projected costs for 2025 assume business as usual, says Mandell. “In some ways, they offer us a doomsday benchmark,” he says. “They’re saying if we don’t get better at helping adults with autism and keeping them in their communities, if we don’t get better at delivering efficient, cost-effective care, then the economic toll is only going to increase.”

The researchers do consider a more optimistic scenario: If current spending on behavioral interventions for children with autism halves costs for young adults in 2025, then the cost of autism would drop by roughly \$28 billion.

Optimizing these interventions for individuals could further lower costs. The new study budgets for expensive one-on-one interventions, which not all children need, says Connie Kasari, professor of human development and psychology at the University of California, Los Angeles.

“The cost of autism is huge, so we need to think about where we’re putting our energy. We need to improve those services in schools because those are the services for the majority of kids,” she says.

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This article was originally published in 2015.

# 3

## All Rise

*Epidemiologists around the world have charted trends in autism. The indicators all point in the same direction: up.*

Prevalence studies performed over the past 25 years have disagreed on a lot, but two findings have been remarkably consistent: a roughly fourfold higher occurrence of autism in boys than in girls, and estimates that climb over time.

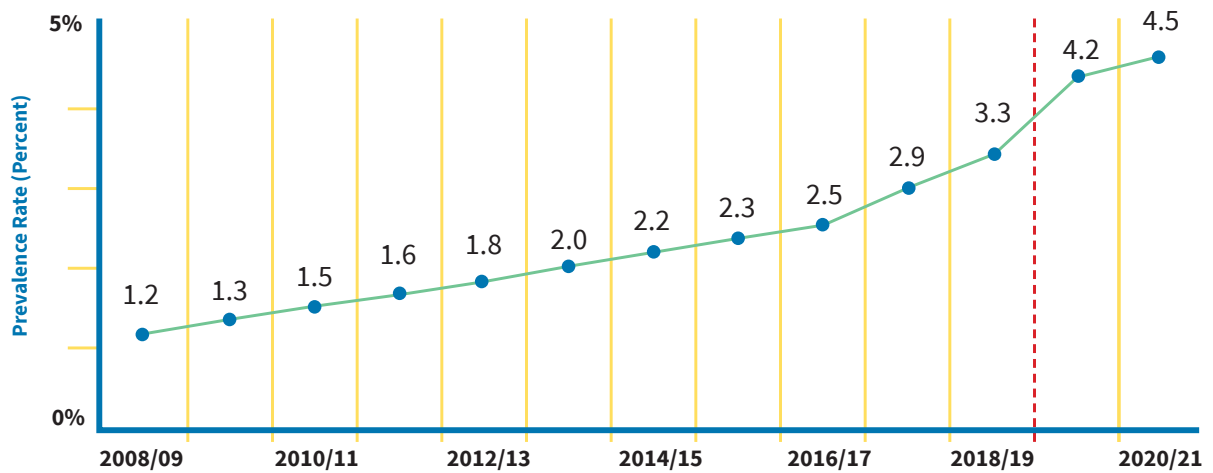
“Autism seems to be on the increase,” the pioneering psychiatrist Lorna Wing wrote back in 1996 in an article for the *British Medical Journal*. Reviewing reports of increasing case numbers, she questioned whether “the impression that there is a rise could be due to a change in referral patterns, widening of diagnostic criteria for typical autism (which are difficult to apply with precision anyway), and increased awareness of the varied manifestations of disorders in the autistic spectrum (especially those associated with higher IQ).”

Researchers in other countries soon noticed the phenomenon as well. The next year, researchers at Sahlgrenska University Hospital in Gothenburg, Sweden reported that 0.07 to 0.55 percent of all children age 3 to 6 in the nearby town of Mölnlycke met narrow diagnostic criteria for autism (excluding what was then known as Asperger syndrome, which diagnostic manuals now include as a part of the autism spectrum). Those rates—though quite low by current norms—were “considerably higher than in previously published reports,” the authors wrote, noting that they had probably missed cases that would eventually appear as children entered school.

A follow-up study by one of the same authors screened all 826 children born in 1985 who were living in Karlstad, Sweden in the fall of 1992. Using a broader definition of autism closer to the one commonly used today, the team examined half of the children individually, as well as each child who screened positive. The results—a prevalence of 0.58 to 2.3 percent, and a boy:girl ratio of 8.5:1 that suggests some autistic girls were overlooked—were markedly higher than those for Mölnlycke but right in line with rates seen more recently.

### LEARN MORE

For details on the lopsided sex ratios observed in autism studies and how they may have overlooked girls, see “Autism’s Sex Ratio, Explained” on page 72 and “For Girls, the Path to an Autism Diagnosis Is Filled with Hurdles” on page 74



Northern Ireland’s annual school census has found that the fraction of students who have an autism diagnosis has shot up over the past 13 years. Changes in data-collection methods in the 2019/2020 school year mean that the two most recent figures are not directly comparable to those for earlier years. But the estimate suggests that more than 4 percent of children overall are on the spectrum.

By 2003, a decade later, Fombonne was cautioning in the *JAMA* that the CDC’s reported number of 0.34 percent prevalence for autism among 3- to 10-year-old children in the metro Atlanta region was “likely to be an underestimate.” (The most recent range from the ADDM for its Atlanta site is 1.7 to 2.1 percent.)

Plotted over time, the five sets of autism prevalence measurements that the U.S. government publishes may not agree in number, but they all point in the same direction: ever upward. “I used to think it was going to plateau at 1 percent,” Durkin says. “Obviously that didn’t happen.”

What did happen in Brick Township and Karlstad has now become a global phenomenon. More children than ever before are being diagnosed in China and Greece, in Denmark and the United Kingdom. Autism, once regarded as rare, is today estimated by some surveys to be at least 10 times as common as blindness or Down syndrome and

twice as prevalent as congenital heart defects. The most recent estimates show roughly double the number of children in the U.S. and Canada living with autism as live with moderate-to-severe hearing loss. In fact, that prevalence of 0.67 percent that was measured in Brick Township 20-odd years ago—a rate so high that some parents there worried for the safety of their children—would now be considered well below average.

In Northern Ireland, public-health officials conducted a complete census of school-age children and reported in May 2021 that a whopping 6.7 percent of boys and 2.2 percent of girls have received a formal autism diagnosis. Equally surprising is the steepness of the trend there: The fraction of children age 4 to 16 with autism has shot up over the past 10 years from 1.5 percent to 4.5 percent.

In interviews and articles, Fombonne has repeatedly cautioned that these apparent increases

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<https://prevalence.spectrumnews.org/>

could be illusory, for a variety of reasons we will soon explore. But studies he has worked on contribute to the picture of a global rise in autism—illustrated by *Spectrum's* interactive map and timeline of prevalence studies at <https://prevalence.spectrumnews.org/> and the graphic on page 89.

In South Korea, for example, Fombonne helped Young Shin Kim with a widely cited community study of around 55,000 school-age children in the city of Goyang. In a 2011 paper—which used methods that the authors acknowledged as imperfect—they reported finding that 1.9 to 3.4 percent of the children were on the spectrum.

Fombonne recalls that the head of child psychiatry for South Korea at the time told him he was welcome to do the study, “but you know, Dr. Fombonne, we don’t have autism in this country.” Korean culture then stigmatized autism; “it would reflect badly on their whole pedigree,” Fombonne says, to the point that a diagnosis would threaten marriage prospects for relatives, autistic or not, on both sides of the family. After the revelation that so many South Korean children have autism, that stigma has faded, he says.

Shih and Fombonne teamed up with Hao Zhou and a large research team in China to study more than 125,000 schoolchildren in Shanghai, Beijing and six other large cities from 2014 to 2016. Using screenings and evaluations, they estimated the prevalence of autism to be 0.87 to 1.0 percent in boys and 0.26 to 0.34 percent in girls. As in South Korea, a large fraction of those with autism—here, about 43 percent—had not previously been diagnosed.

Another study, published in 2019, screened children in every main-stream and special-ed school in Jilin City, China and also looked for children not attending school. They obtained an estimated overall prevalence much closer to that often seen in Western countries: 0.87 to 1.4 percent.

In the Middle East, some governments still tend to conceal developmental conditions,



including autism, but reported numbers there, too, are ticking upward. In Iran, a recent study, on which Fombonne was a senior investigator, suggested that autism was present in just 0.13 percent to 0.22 percent of the 30,500 children included. That's a striking contrast to the results of a far more comprehensive study in Qatar (also coauthored by Fombonne) that covered 177,000 school-age children and found autism in 0.89 percent to 1.46 percent—in line with estimates from the U.S. and Europe.

To understand what to make of such head-scratching numbers, I visited the University of Washington's Institute for Health Metrics and Evaluation (IHME), perched next to the monorail in downtown Seattle. This place has become famous for its Global Burden of Disease study, or GBD. Every year, the GBD issues a report card on the health of humanity, plotting the ups and downs of hundreds of different diseases, injuries and disabilities in 204 countries and territories. Using sophisticated supercomputer models and advanced statistical methods, researchers here do their best to correct for missing and biased data in public-health surveillance systems.

I sat down in a conference room with Theo Vos and—joining us by video from his office in Brisbane, Australia—Damian Santomauro. They help assemble and supervise the sections of the GBD that track autism and other developmental disabilities. I asked them about the high prevalence numbers coming out of places like Northern Ireland, New Jersey, and South Korea.

“That’s incredible,” Santomauro said as he scanned the Northern Ireland data, which he had not yet seen. His two big worries: First, that the high numbers might be right; and second, that they might be very wrong.

The GBD's most recent estimate of autism among boys age 5 to 14 in Northern Ireland is 1.1 to 1.6 percent—about a quarter of what the health authorities reported there. So if the official numbers are correct, then the GBD—considered by many the most rigorous and methodologically advanced compilation of prevalence data—is way off.

#### LEARN MORE

For more details on prevalence studies in the United Kingdom, South Korea, Vietnam, India, and other nations, see Part II: A Global Phenomenon on page 70.

Northern Ireland aside, there are other possible explanations for such trends, Santomauro and Vos suggest. It could be that doctors, having long overlooked children with autism, are now erring in the other direction and overdiagnosing children. Newer numbers from countries like the U.S. that lack national healthcare systems may be based on unreliable screens or parental reports of a child's

Blindness and deafness have clear, easy-to-measure diagnostic criteria, rooted in biological function. Yet even for those conditions, the criteria have shifted as technology and society have evolved to accommodate people with impaired sight or hearing. The practice of diagnosing autism has evolved much more: It wasn't until 1980 that autism got its own entry in the Diagnostic and Statistical

*“That’s really alarming,” Santomauro said as he scanned the Northern Ireland data. His two big worries: First, that the high numbers might be right; and second, that they might be very wrong.*

behavior, which are known to be less accurate than actual diagnoses. Even in places that maintain nationwide health registries, “the sources on which registries base their numbers may have changed over time,” Vos says. Or it may be that estimates calculated by examining small, unrepresentative groups of children are being extrapolated incorrectly to the general population.

And there are more possibilities still. As we will see in Chapter 6, measuring the true prevalence of autism is an inherently difficult—maybe even impractical—thing to attempt because “awareness among the public and health workers has changed,” Vos says. “This is an issue with all the mental disorders that we model,” Santomauro notes.

At the root of the issue is the concept of autism spectrum disorder. “Autism,” Durkin points out, “is definitely a socially defined condition.” By that she means that human beings exhibit a huge range of characteristic behaviors, and societies have decided to draw boundaries around some of those and call them ‘autism.’

Manual of Mental Disorders (DSM), which sets standards for neuropsychiatric diagnoses that drive insurance coverage. Before that, autistic people were recorded as having child-onset schizophrenia, and the measured prevalence was effectively zero.

Those behavioral boundaries that societies draw shift from place to place and generation to generation, in response to changing knowledge, technology and other prods. In the U.S. and other advanced countries, developmental differences and disabilities that were once concealed or ignored are now more accepted—and visible.

The observed prevalence of autism reflects public awareness, diagnostic criteria and availability of services, and “all that has been changing,” Durkin observes. “It doesn’t necessarily mean there’s something in the air that’s causing this.”

But the flip side is true as well. Sociological forces do not necessarily rule out biological ones that could be steering an increasing fraction of children onto autistic developmental paths.

# NEW STUDIES FIND MORE AUTISTIC PEOPLE IN CHINA

BY PETER HESS

*Autism was thought to be rare in these countries.*

*New studies, though still imperfect,  
conclude that it is roughly as prevalent  
there as it is in other nations.*

About 0.7 percent of children in China aged 6 to 12 have autism, suggests the largest study of the country's autism prevalence to date<sup>1</sup>. And in Greece, 1.15 percent of 10- and 11-year-olds have the condition, according to the first estimate for that country<sup>2</sup>.

Both figures fall within the range of autism prevalence estimates reported for children in other nations. The studies also show that autism is about four times as common in boys as it is in girls in both countries, a ratio in line with studies of children in the United States and elsewhere.

A 2019 study of 45,036 children in three Chinese cities came up with a slightly higher estimate of about 1 percent. But the new work includes almost three times as many children, from eight cities, and may better represent China's population, the researchers say. It also provides the first data on the prevalence of co-occurring conditions, such as attention deficit hyperactivity disorder, phobia or obsessive-compulsive disorder.

"It's a very strong starting point, and it's a step up for China compared to what was there before," says Eric Fombonne, professor of psychiatry at Oregon Health and Science University, who helped design the study, a collaboration among researchers across five provinces and three municipalities—groups that often compete for government research funding. "These epidemiological studies are behemoths, very difficult to do."

Still, the new studies may underestimate the actual number of children with autism in China and Greece.

Autism prevalence research in both countries is in early stages compared with prevalence research in other

countries, says Mayada Elsabbagh, assistant professor of neurology and neurosurgery at McGill University in Montreal, Canada, who was not involved in either study. Instead of true prevalence, the new estimates in China and Greece likely reflect levels of community awareness, the quality of services and the availability of diagnostic tools, she says.

## IDENTIFYING CHILDREN:

Fombonne and his colleagues used government records to identify 125,806 eligible children ages 6 to 12 living in eight Chinese cities, chosen as a representative sample of the country. To screen the children for autism, the team distributed a questionnaire they had developed, called the Modified Chinese Autism Spectrum Rating Scale (MC-ASRS), to parents and teachers.

The MC-ASRS screen flagged 37,500 children. After group interviews with the children, the team offered diagnostic evaluations to 1,135 of them; about 20 percent of the children's families declined. The team also evaluated children attending special education schools, who they assumed were more likely to be autistic.

Of the 1,079 of children evaluated for autism, 363 met criteria for the condition. Forty-three percent of the children had not been previously diagnosed, and more than 90 percent of these children attended mainstream schools. By assuming that the prevalence numbers for children from nonresponsive families would be roughly the same as those for the rest of the participants, the researchers estimated an overall prevalence of 1 in 143.

This figure falls on the lower end of the range reported for other countries, suggesting that more children remain to be identified in the region, Elsabbagh says. "It's nevertheless a very useful tool to get kind of a screenshot of the current situation of autism in China, and certainly a useful estimate in terms of informing policy and services."

The study shows that 69 percent of autistic children in China have at least one co-occurring neuropsychiatric condition, the most common of which is attention deficit hyperactivity disorder, identified in 43 percent of them. Medical records for about 30 percent of the children showed that the most common co-occurring physical

conditions are gastrointestinal problems, sleep disorders, allergies and seizure disorders.

The inclusion of data on co-occurring conditions is a welcome contribution of the study, Elsabbagh says. “Here the picture is somewhat consistent with some of the reports we get from other countries.”

#### EARLY STEPS:

The Greek study, the first large-scale autism prevalence study in that country, relied on education records to determine the autism status of 182,879 children. It shows a prevalence of about 1 in 87.

The approach appears to achieve good coverage of the country’s 10- and 11-year-olds, yielding results that line up closely with other autism prevalence estimates, Elsabbagh says. But, she adds, “one could argue the use of data that doesn’t involve doing direct assessments is problematic.”

The numbers would likely be more reliable if researchers had done follow-up clinical interviews with children, Fombonne says. Unlike the Chinese study, the Greek study does not include data on co-occurring conditions, but the researchers present a fair and accurate picture of the limitations of their findings, he says.

*Spectrum* could not reach the researchers behind the Greek study for comment.

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This article was originally published in 2020.

# How Routine Screening Transformed the View of Autism in Oman

BY LAURA DATTARO

*In 2010, the country had just one developmental pediatrician. But then she championed a national program to examine all toddlers for signs of autism.*

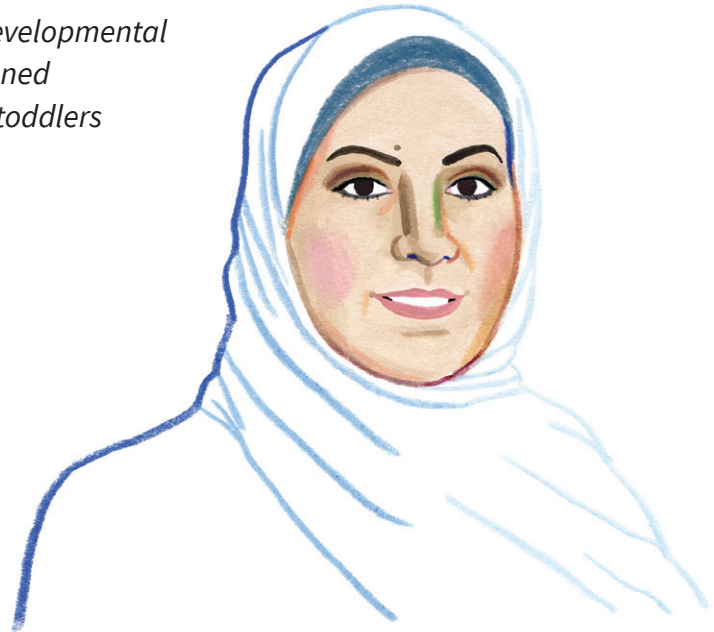


Illustration by Rebecca Clarke

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A new study has found that 0.2 percent of children in Oman are on the autism spectrum<sup>1</sup>. This estimate is about 15 times higher than a 2011 finding, the only other study of autism prevalence in the country.

The jump in prevalence probably reflects Oman’s targeted efforts over the past five years to diagnose, treat and raise awareness about autism. In 2017, the country launched a national screening program, requiring all children to be screened for autism at 18 months when they receive their compulsory measles-mumps-rubella vaccines<sup>2</sup>. Clinicians then refer children to diagnostic centers and services as needed.

“This difference in 10 years is telling us something,” says lead investigator Watfa Al-Mamari, developmental pediatrician at Sultan Qaboos University in Muscat, Oman. “We need to work more; we should screen more.”

The 2011 study found only 113 children with autism in the entire country, at a prevalence of 1.4 cases per 10,000 children. Researchers identified the children after reviewing medical records and surveying parents.

For the new analysis, Al-Mamari and her colleagues reviewed records from 2011 to 2018 for children aged 0 to 14 years at Oman's three main autism diagnostic centers: Sultan Qaboos University Hospital, Royal Hospital and Al-Masarra Hospital. All three centers are located in or near the country's capital of Muscat.

They identified 1,705 children with autism from among 837,655 children. The prevalence in Omani boys is nearly four times higher than in girls, which is in line with estimates from other countries.

The prevalence of autism is highest in Muscat,

bagh, associate director of the Azrieli Centre for Autism Research at McGill University in Montreal, Canada, who was not involved in the research.

“Hopefully, that message could provide further motivation for policymakers in Oman and elsewhere to continue along this path and increase further capacity,” Elsabbagh says. “There’s a big mismatch everywhere in terms of the needs for those affected versus the available services in those countries.”

As part of the Oman-wide program launched in 2017, Al-Mamari led efforts to create screening materials in a dialect of Arabic spoken by most peo-

### *Al-Mamari led efforts to create screening materials in a dialect of Arabic spoken by most people in the country.*

at about 0.37 percent; it drops as low as 0.04 percent in regions farther from the diagnostic centers, suggesting that the prevalence in these regions is an underestimate.

“Historically, it has always been very useful to look at the prevalence of a condition, even though you know your methods might underestimate the magnitude of the problem,” says Eric Fombonne, director of autism research at the Institute on Development and Disability at Oregon Health and Science University, who was not involved in the study.

#### A FOCUS ON AUTISM:

The latest reported prevalence of autism in the United States is 1 in 59 people. That figure has been plateauing over the past few years as awareness of the condition has increased.

The increased prevalence in Oman may also reflect improved services there, says Mayada Elsabbagh,

ple in the country.

The new survey found a higher prevalence in younger children than in older ones. The researchers identified 30.34 children with autism per 10,000 children aged 0 to 4, compared with 4.52 children aged 10 to 14 years. Fombonne says this variation may be due to the fact that younger children are benefiting from the new programs and rising awareness of the condition—and that the trend suggests autism prevalence estimates in Oman are likely to rise again.

#### THE WOMAN WHO LAUNCHED OMAN'S SEARCH FOR AUTISTIC CHILDREN:

When Watfa Al-Mamari first returned to her home country of Oman in 2010 after six years at a medical residency in Canada, her skills were in unique demand: She was the only developmental pediatrician in the country.

Al-Mamari immediately went to work raising awareness within the government about autism and developmental delays and establishing services for children with those conditions. She created screening and diagnostic materials for autism in the Arabic dialect most commonly spoken in Oman. Her efforts ultimately led to the 2017 launch of a national screening program for autism, which requires all children born in the country to be evaluated at 18 months.

She also set out to determine the prevalence of autism in Oman<sup>1</sup>. In December, she and her team reported that the prevalence is 0.2 percent, representing a 15-fold increase over the previous estimate of 0.01 percent, published in 2011.

Al-Mamari spoke to *Spectrum* about what this increase means and why the program is so crucial for Omani children.

**SPECTRUM:** *How does Oman's new screening program for autism work?*

**WATFA AL-MAMARI:** Oman decided in 2017 that the program should be compulsory routine screening. The mumps-measles-rubella vaccine usually is given here at 18 months of age, and it's not optional. So when the children come for their 18-month vaccine, they also go through the screening. A trained doctor or senior nurse administers the screening questionnaire. They go through it and explain it as much as possible to the parents who fill it out. There are three main centers in Oman where children with a positive screen can be referred to. After the diagnosis, the children will receive services in their region.

**S:** *What was your role in establishing the screening program?*

**WA-M:** I started working on the screening program when I first came from Canada with some medical students. I launched the first developmental clinic in the country. And I was trying to find a way to get these young children diagnosed as early as possible because we felt we were missing a lot of them. That 2011 paper, which stated a very low prevalence of 1.4 in 10,000, was that really real? So I really worked on it with my team. It was not an easy task, and then to discuss this kind of program and to convince also the governmental sectors, that definitely took time. We are just a very small team of three doctors and a nurse and a social worker. I really led the group with another person from the Ministry of Health, and we went from there—and here you go: Now it's a routine program in the country, and every child has to go through it. It was a big thing in the country.

**S:** *What prompted you to look at the prevalence of autism across the whole country?*

**WA-M:** I think in many parts of the world, developmental pediatrics is a rare specialty. But now the numbers have increased, and it is reflected in the prevalence that has also increased. The 2011 paper's estimate was considered to be very low compared with other parts of the world, but that could be for so many reasons. At that time, most of the tools for assessment, screening and diagnosis were mainly in English. The language was a barrier. But with increasing awareness and with media attention, things have changed everywhere. The same was [true] here. The increase in diagnostic centers and in services in the country gave us an opportunity to

look again at the prevalence. We thought we should look at that number because having that very low previous prevalence definitely affected so many things—the services, the strategy planning for autism, everything.

**S:** *What practical problems did you have to solve?*

**WA-M:** Honestly, it took a lot of time. Our study was originally just a pilot study using the formal Arabic language. It was really inaccurate and not usable. Also, from one country to the other Arabic is so variable. We did many pilot studies over many years to come up with the most suitable Arabic version. We even took an idea from the Japanese experience. Their screening tool uses pictures to help people understand the questions better. That's why our version has not only the regular questions but also the pictures. The screening program has increased the number of children who are diagnosed before 3 years of age. So that's having a difference in terms of the early intervention, the amount of services. It has really helped us a lot.

**S:** *From your study, the prevalence now seems to be higher in younger children than in older ones. What might explain that difference?*

**WA-M:** When we first started the program, the older children used to have more diagnoses because of records from schools, different health centers, things like that. But the national program has influenced the age of diagnosis. Children get to be screened earlier, at younger than 2 years of age. That's why it's now higher in children under 5 years of age than in older children.

**S:** *What's next for your research?*

**WA-M:** There are many implications for the new prevalence on autism strategy planning and services distribution. Yes, the new study is showing a different figure compared with the previous one. Still, if you compare it with the international figures, you can see that there is a gap; there is a difference. Autism now, according to the [U.S. Centers for Disease Control and Prevention], is much higher than this. We are planning to establish a more widespread national screening, at different age levels, so we can come up with far more, because this is alarming. This difference in 10 years is telling us something: that we need to work more.

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This article was originally published in 2020.



# Changes in Brains

# 4

*The search for biological agents that could explain part of the rise we've seen in autism numbers has ruled out vaccines. But other factors—from increases in preterm births to aging parents—remain under investigation.*

So let's look at those factors that are rooted in biology: things like environmental exposures, medical practices, even population genetics. Though myriad factors have been linked to the origin of autism, the question we're asking is not about the reasons that autism exists, but why it seems to be so much more common than it used to be.

Vaccines have been thoroughly investigated and ruled out as a cause, but for most other suspects, the evidence is still highly circumstantial, according to a 2017 review from an international team of collaborators.

Take parental age, for example, which the review found is one of the most consistently identified risk factors for autism. Three studies—a 2008 examination of ADDM data by Durkin and others, a 2009 analysis of all singleton babies born in California from 1989 to 2002, and a 2016 review of data on almost 6 million children born in Denmark, Israel, Norway, Sweden and Western Australia—all came to similar conclusions: “Each parent’s age has an independent effect,” Durkin says. In those studies, babies born to women over 40 or to men over 50 faced a small but statistically significant increased likelihood of developing autism—with the exception of those in Israel, where risk oddly seemed to *decline* with advancing parental age.

The association is interesting because both men and women have been conceiving children later in life since the 1980s. Fertility rates

among American women age 40 to 44, for example, tripled between 1980 and 2017.

But is age really the causal factor—perhaps acting, Fombonne suggests, through mutations that build up year after year in the reproductive cells of older parents? That could be, but there is another possibility.

“An obvious thing that might cause this,” Durkin says, “is if the parents themselves are on the autism spectrum.” Autistic parents might tend to meet and mate later in life than neurotypical people do, she suggests.

If so, that could make it look like parents’ ages at conception increase the chance of having an autistic child, when in fact what really matters is whether they are themselves on the spectrum. Autism, after all, is highly heritable: Estimates range from 50 percent to 95 percent. It runs in families about as strongly as height and baldness do among white men.

The high heritability of autism has other interesting implications as well, Durkin observes. If women on the spectrum tend to pair up with autistic men as partners, and vice versa, then regardless of the age at which they have children, that pattern of ‘assortive mating’ could nudge the prevalence of autism upward over time in two ways. First, each parent might contribute a

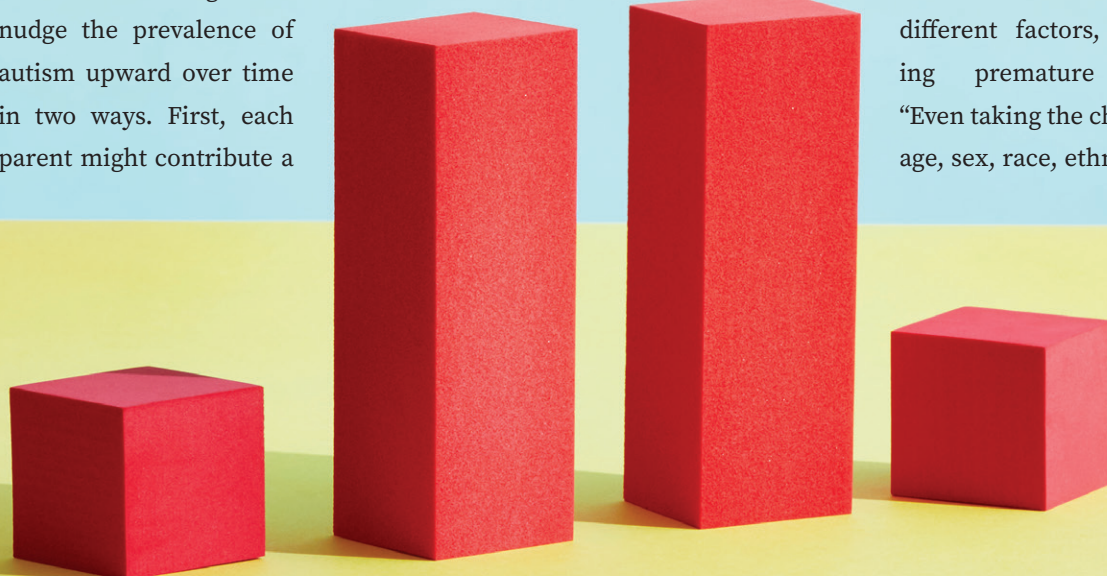
genetic predisposition toward autism, increasing the likelihood that any of their children will have the condition. And second, their awareness of autistic traits might make it more likely that their autistic children get a diagnosis.

If this phenomenon hasn’t already contributed to the uptick in prevalence, it may well do so in the near future. More adults now know that they are on the spectrum, and it’s become easier than ever for them to find a partner of like mind through online support communities.

Because autism probably originates in how the brain develops, it makes sense that difficulties during pregnancy or childbirth could play important roles (see “How Pregnancy May Shape a Child’s Autism,” page 96). So far, multiple large-scale studies have reported statistical links to autism from maternal diabetes, serious prenatal infection and premature birth.

At the HRSA in Rockville, I sat down with Michael Kogan, who has overseen the National Survey of Children’s Health since 2003, and we looked at the strong connections that survey has revealed

between autism and many different factors, including premature birth. “Even taking the children’s age, sex, race, ethnicity, et



cetera—taking all that into account—if a child was born preterm, they’re still 71 percent more likely to have received an autism diagnosis,” he says, than a child delivered after at least 37 weeks of gestation. ADDM data show something similar.

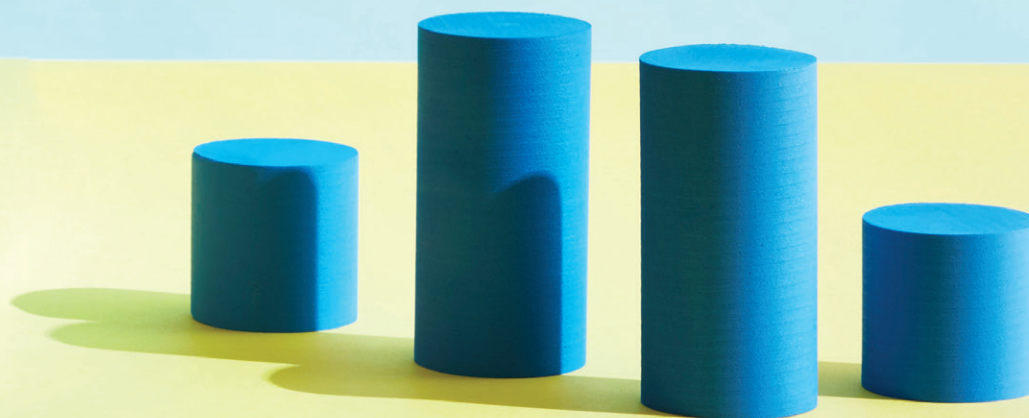
That association could also help to explain the increase in autism prevalence: Thanks to advances in medical care, doctors now routinely rescue more than half of babies born up to 13 weeks preterm. Extreme preemies survived less often in decades past (see “Improved Care for Premies May Contribute to Higher Autism Prevalence,” page 105).

Maternal diabetes is one of the strongest factors linked to increased autism chances, says Irva Hertz-Picciotto, an environmental epidemiologist in the MIND Institute at the University of California, Davis. Babies born to mothers having type 2 diabetes—the more common form—are at nearly a 40 percent increased chance of having autism, according to a large 2018 study by a group at Kaiser Permanente. That study also found that infants born to mothers who have type 1 diabetes seem to be roughly twice as likely to have autism as children born to women without the condition. “There [are] very consistent data from really superlarge studies that, to me, make it a pretty compelling story,” Hertz-Picciotto says.

That diabetes link, too, could be helping to buoy autism prevalence upward: The incidence of both type 2 and gestational diabetes (a temporary form that develops during pregnancy) has soared in recent years, driven by sedentary lifestyles, sugar-rich diets and obesity. And thanks to improved treatments, more women with type 1 diabetes—the insulin-dependent, autoimmune kind—can become mothers than before.

Bobbie Gallagher’s worry was that she and her children in Brick Township had been exposed, like those in neighboring Toms River, to DNA-damaging environmental toxins while she was pregnant. Though many possible toxins have been tenuously linked to autism, numerous studies have turned up very little evidence that could explain soaring autism prevalence. As Hertz-Picciotto points out, “the causes of the *rise* are not necessarily identical to the causes of autism as a whole.”

Hertz-Picciotto has spent years investigating whether pesticides, air pollution, heavy metals and other kinds of environmental toxins might be contributing somehow to that rise. But the science is bedeviled, she says, by the almost overwhelming complexity of how environmental insults affect mothers-to-be, plus the myriad biological systems at work in brain development.



As with most noninfectious disease, there is “a web of causation,” she says. “You can’t boil it down to one factor and, in most cases, not even one [physiological] pathway.” Environmental insults are offset or exacerbated by genetic predispositions; infections and fevers get thrown in the mix; timing can be everything.

Pollutants, for example, might affect autism rates through the slow accumulation of small

are more exposed to a compound during gestation or infancy, researchers must also show that that exposure has been growing and that it is biologically tied to brain development. That’s a tall order when many suspected environmental toxicants, such as PCBs, phthalates, air pollutants and heavy metals, are nearly ubiquitous—and in many areas have actually been declining.

**“The causes of the rise  
are not necessarily identical  
to the causes of autism  
as a whole.”  
— Irva Hertz-Picciotto**

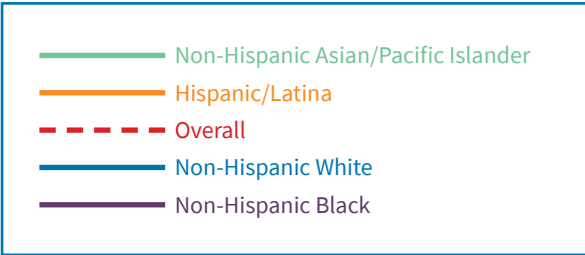
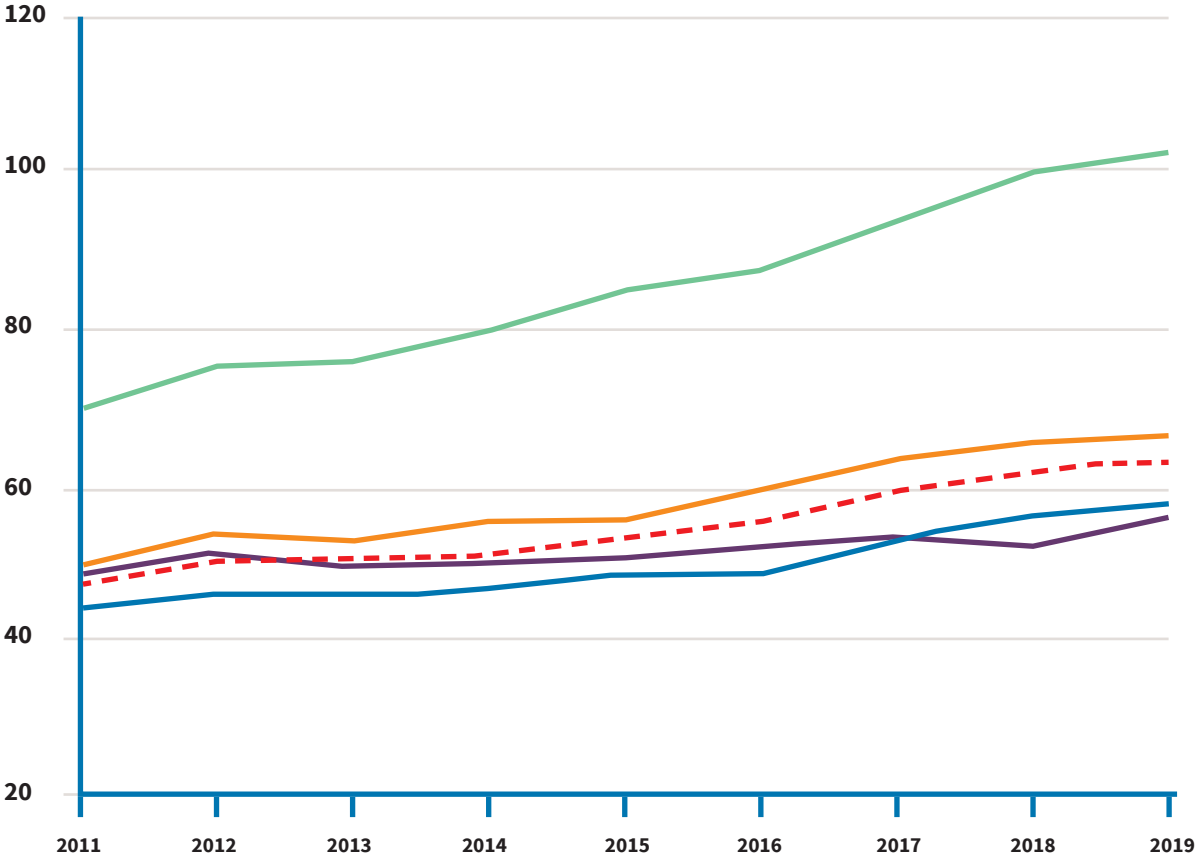
insults to parents’ reproductive systems, Fombonne notes. Some environmental toxins are known to be mutagens, meaning they can mutate the DNA in the reproductive cells that eventually make babies. Other pollutants are so-called endocrine disruptors that interfere with the hormones that regulate our reproductive systems. The longer parents delay childbearing, the more their bodies are at risk of such damage.

It’s difficult, however, to build a convincing case that pins increases in autism on particular pollutants. In addition to showing that autistic children

Durkin and Fombonne, as well as other researchers, have run the numbers for some of the most established environmental influences, such as advanced parental age, to estimate the size of their contribution to the autism epidemic. For parental age, Durkin says, “it’s a very tiny percent. I mean, it’s only like single digits.” If that’s true for other biological factors as well, as now seems likely, that suggests that the bulk of the phenomenon originates not with autism itself, but with the ways society defines and diagnoses it.

# GESTATIONAL DIABETES RATE PER 1,000 LIVE BIRTHS

Gestational diabetes has been rising dramatically in the United States and many other countries. Some studies have found that babies born to women with diabetes are more likely to be later diagnosed with autism.



Source: Shah et al., JAMA (2021) DOI:10.1001/jama.2021.7217

# WHY MIGHT OLDER PARENTS BE MORE LIKELY TO HAVE AUTISTIC CHILDREN?

BY SARAH DEWEERDT

*Answers may lie in their sperm and eggs—  
or in the tendency of people on the spectrum  
to start families later in life.*

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.

This article was originally published in 2020.

# IT'S PROBABLY NOT SOMETHING IN THE WATER OR THE AIR

BY PETER HESS

*Genetics outweigh environmental factors, says a big study of autistic twins.*

The relative contributions of genetic and environmental factors to autism and traits of the condition have held steady over multiple decades, according to a large twin study<sup>1</sup>.

Among tens of thousands of Swedish twins born over the span of 26 years, genetic factors have consistently had a larger impact on the occurrence of autism and autism traits than environmental factors have. The study suggests that genetics account for about 93 percent of the chance that a person has autism, and 61 to 73 percent of the odds she shows autism traits.

The figures fall in line with previous work that shows genetics exert an outsized influence on autism odds. The findings also indicate that environmental factors are unlikely to explain the rise in autism prevalence. Otherwise, their contribution to autism among the twins would have also risen over time.

“I think the relative consistency of the genetic and environmental factors underlying autism and autism traits is the most important aspect of this work,” says Mark Taylor, senior research specialist at the Karolinska Institutet in Stockholm, Sweden, who led the study. “Prior to our study, there had been no twin studies examining whether the genetic and environmental factors underlying autism had changed over time.”

## FAMILY FACTORS:

The researchers analyzed data from two sources: 22,678 pairs of twins in the Swedish Twin Registry, who were born from 1982 to 2008; and 15,280 pairs of twins from the Child and Adolescent Twin Study in Sweden, born from 1992 to 2008.

The team divided these groups into cohorts according to when the children were born. They created five birth cohorts from the registry group and four from the study group. The cohorts include both fraternal and identical twins. Identical twins share nearly all of their genetic code, whereas fraternal twins share an average of 50 percent. In the registry group, about 24 percent of the twin pairs are identical; in the study group, almost 30 percent are identical.

Among these twin pairs, they identified children with autism and confirmed the diagnoses, either by using health records and case notes, or via phone interviews with parents or caregivers. Also by way of phone interviews, they identified twins in the study group who display autism traits but do not meet the criteria for a diagnosis.

To estimate how much genetics or the environment had contributed to autism in both groups, they compared differences between identical and fraternal twin pairs—looking specifically at how often one or both twins were affected. Then they looked at whether these proportions changed from one birth cohort to the next.

In all of the birth cohorts, there are more identical twin pairs than fraternal ones in which both twins have autism or show autism traits. The work appeared in *JAMA Psychiatry*.

The pattern suggests that genetic factors hold more sway over autism than environmental ones do. If the reverse were true, there would be more behavioral similarities between fraternal twins.

## TWIN ISSUES:

Some experts question whether twin studies—even large ones like this—can offer definitive answers.

The origins of autism may involve an interaction between genetics and the environment, which twin studies do not capture, says Brian Lee, associate professor of epidemiology and biostatistics at Drexel University in Philadelphia, Pennsylvania, who was not involved in the study.

“Asking whether genetics or environment is more important is the wrong question,” Lee says. “To me, it’s sort of like asking whether it’s more important to put on your left shoe or your right shoe to go out in public.”

The new study is well designed and conducted but, given the limitations of twin studies, may not add much



to previous work to clarify the relationship among environment, genetics and autism, says Joachim Hallmayer, professor of psychiatry at Stanford University in California, who was not involved in the study.

“It’s probably as good as these studies in our field can get,” he says.

Taylor disagrees and says the findings could shape the discussion over rising autism prevalence figures.

“[This study] emphasizes that despite the rate of autism diagnoses increasing, really not much appears to have changed in the underlying etiology,” he says.

Next, the team plans to focus on specific environmental factors they previously linked to autism to see if those contributions have changed over time. They also plan to look at other neurodevelopmental conditions that have become more or less prevalent.

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This article was originally published in 2020.

# 5

## Changes in Society

*Doctors and epidemiologists are getting better at recognizing autism traits. But in the U.S. and many other countries, health professionals still fail too often to identify autism early and accurately.*

It's easy to underestimate the power of changing perspectives and shifting incentives. The history of medicine is filled with stories of conditions that were practically unheard of until doctors began looking for them—and then gradually discovered them to be shockingly common. That was the story of celiac disease, for example, which during the 20th century was diagnosed exceedingly rarely and almost exclusively in children. We know now that it affects something like 1 percent of adults. Psychiatrists similarly dismissed depression as essentially nonexistent in young children decades ago. Now around 3 percent of American children have a current diagnosis. With autism, too, pediatric practice has shifted dramatically in ways that steadily add to the counts of those on the spectrum.

In 2007, for example, the American Academy of Pediatrics changed its recommendations in a highly influential but hotly debated decision to urge pediatricians to screen all children for autism at age 18 months and again at age 2. You can see the effects of that policy clearly in numbers *Spectrum* obtained in 2019 from California's Department of Developmental Services (DDS) (see "The Biggest Factor Behind California's Exponential Rise in Autism Might Be Pediatricians" on page 42).

Each year during the early 2000s, the number of people served by the agency who had an autism diagnosis had increased by 2,000 to 4,000. But in the year after the academy called for routine screening, the number of DDS clients adding an autism diagnosis jumped from

198 to 1,727, and the number of autistic children in California applying for benefits for the first time more than doubled, to 8,541.

Those numbers surged again starting in 2015, after the Affordable Care Act took effect and extended insurance coverage for autism services to families that previously lacked it. As a result of the accelerating growth in cases, the number of autistic people the DDS serves has skyrocketed, from fewer than 15,000 in 2000 to more than 105,000 in 2018.

When Autism Speaks surveyed academy members a year or two after the 2007 change in recommendations, only about a third of pediatricians said they were following the new guidelines, Shih says. “We’re a lot better now,” with 50 to 60 percent compliance, he says, yet still far from the goal of universal screening.

Outside of the U.S., some countries with universal healthcare systems are closer to that goal, and they have been finding many more autistic children who previously were missed—progress on a problem that epidemiologists term underascertainment. In 2014, for example, the Stockholm Youth Cohort study analyzed records for every child who lived in the capital county of Sweden, a country that screens all children for developmental disorders, between 2001 and 2011. The study found that the prevalence of autism shot up during that decade by nearly three and a half times. In each successive year, the researchers observed, children were diagnosed at younger ages than their older peers had been. And almost all of the increase in prevalence occurred among children who had autism but not intellectual disability. The authors wrote that “a large share” of the observed jump in prevalence probably stemmed from rising awareness of autism and testing for it. But, they added, “we cannot rule

out a true increase in incidence.”

Still, the medical profession, particularly in the U.S., has a long way to go in accurately identifying autistic children, Fombonne says. “There could be a mixture of effects,” he says, in a soft voice lilted with the accent of his native France. “Like this trend is actually going up for good reasons—which is that they are getting better at finding the real phenotype—but then they might also go up for bad reasons: that they are overdiagnosing.”

In one 2019 study of autism screening across 54 pediatric practices and 290 doctors, more than 80 percent of toddlers had been screened at age 2 as recommended. But the doctors had failed to refer children with positive screens to a specialist for evaluation 65 percent of the time. And even when a referral was made, only about two-thirds of the families followed through. Clearly many autistic children could still be falling through the cracks.

Screening tests are also unreliable tools. Another study published that year followed up on all children given physicals after universal screening began at Children’s Hospital of Philadelphia. The results were mixed at best. Though 91 percent of the toddlers had been screened, and 2.2 percent diagnosed with autism—within the ADDM interval estimated for 4-year-olds in nearby New Jersey at that time—the accuracy of the screens was uneven. The test used, known as the M-CHAT, was good at ruling autism out. But when it tagged a child as likely autistic, that prediction turned out to be wrong 85 percent of the time. A different screening method, known as the Social Communication Questionnaire, proved equally unreliable in a recent nationwide study in Qatar: Among cases screening positive, just 9 percent were confirmed in expert evaluations.

## The biggest factor behind California’s exponential rise in autism might be pediatricians

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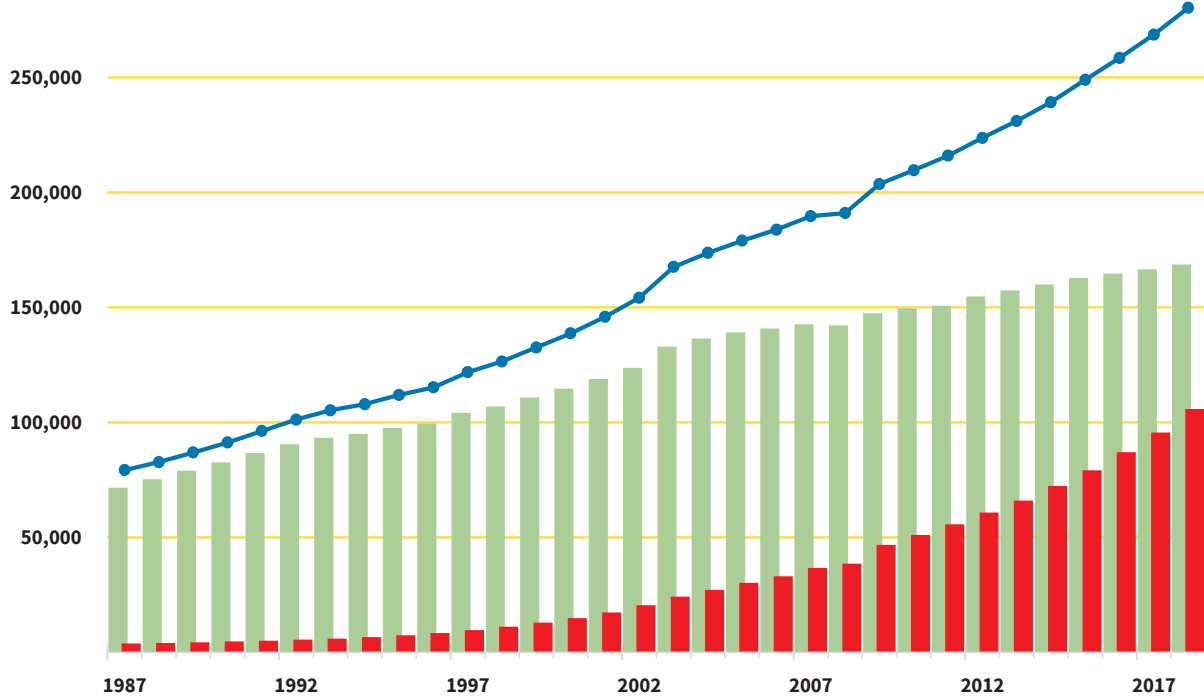
*State data hint that increased screening, rather than diagnostic substitution, has fueled accelerating growth in autism diagnoses.*

Within the United States, California’s Department of Developmental Services (DDS) offers one of the longest and most consistent series of statewide counts of children receiving services for various developmental conditions. The upper chart on the next page shows how the total number of children served by DDS (*blue curve*) has soared since 1987, driven in large part by an exponential increase in the number of DDS clients qualifying for autism services (*red columns*).

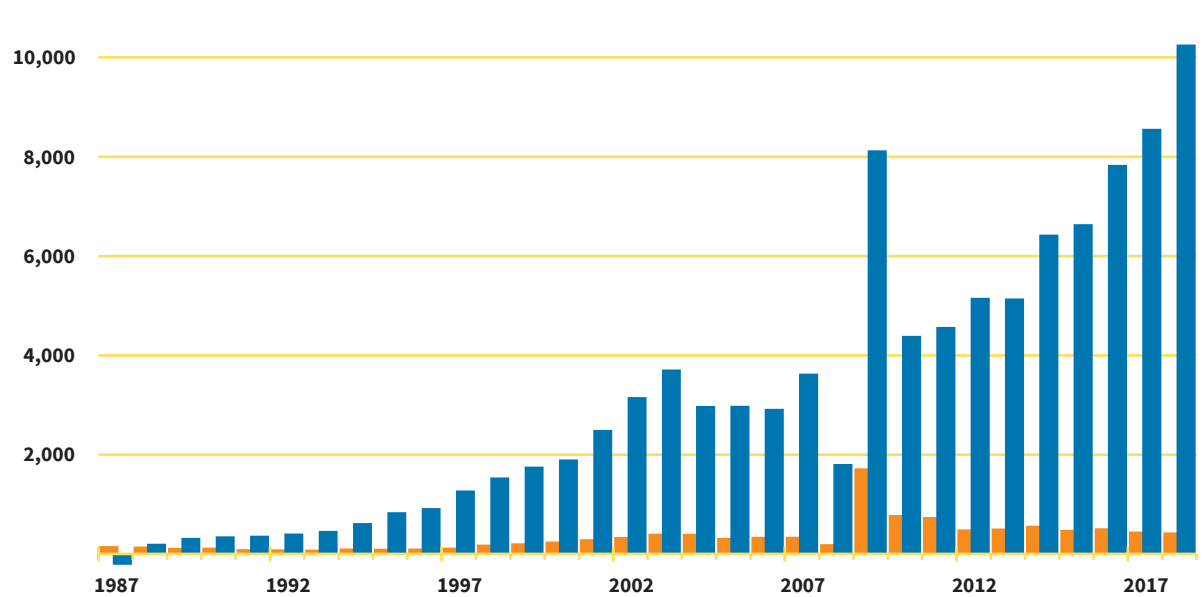
Some of that increase likely reflects diagnostic substitution: children who used to be diagnosed only with intellectual disability now receive a diagnosis of autism instead, or in addition. But as the chart reveals, the number of DDS clients having intellectual disability (*green columns*) has grown, not fallen. So that cannot be the whole story.

Some autism experts have pointed to the changing behavior of pediatricians as a bigger factor. In 2007, the American Academy of Pediatrics called on its members nationwide to begin routine screening of all children for autism. The following year, and a couple years after, California’s DDS saw spikes in both the number of new families requesting autism services (*blue columns, bottom chart*) and the number of existing clients adding an autism diagnosis (*orange columns*).

**AUTISM AND INTELLECTUAL DISABILITY HAVE BOTH GROWN IN CALIFORNIA**



**DDS CLIENTS HAVING A NEW AUTISM DIAGNOSIS SPIKED AFTER THE U.S. PEDIATRIC ACADEMY CALLED FOR ROUTINE SCREENING OF TODDLERS**



## LEARN MORE

For more on how the formal definition of autism has evolved over time, see “The Evolution of ‘Autism’ as a Diagnosis, Explained” on page 128.

*Wider screening, with tests that flag as potentially autistic lots of children who are not, could explain in part why parent polls like the National Survey of Children’s Health and the National Health Information Survey now put the prevalence of autism in the range of 2.4 to 3.2 percent.*

Wider screening, with tests that flag as potentially autistic lots of children who are not, could explain in part why parent polls such as the NSCH and the NHIS now put the prevalence of autism in the range of 2.4 to 3.2 percent.

The exact questions these surveys ask matter, too, because they have changed over time. In 2010, the NSCH and NHIS asked parents whether a doctor ever told them that their child “had autism.” In 2011, that was altered to “has autism or autism spectrum disorder.” Then in 2014, the wording of the NHIS shifted again to “had autism, [Asperger] disorder, pervasive developmental disorder, or autism spectrum disorder.”

There’s nothing nefarious about such shifts, Kogan says. When psychiatrists adopted a new, fifth edition of the Diagnostic and Statistical Manual of Mental Disorders in 2013, they overhauled the formal definition of autism. Asperger syndrome was folded in, along with three other widely used diagnoses. A committee of experts reworded and clarified the diagnostic criteria in ways that seem to have increased autism diagnoses among girls but slightly restricted new diagnoses overall. The updates to the national survey questions reflected a wider evolution in how doctors and society at large have been broadening our definition of autism and how we describe it (see “The Evolution of ‘Autism’ as a Diagnosis, Explained” on page 128).

Nor were they the only changes: As response rates to random-number phone dialing fell, the HRSA pivoted between 2012 and 2016 to using web- and mail-based questionnaires as well for the NSCH. Because you can’t connect dots that represent different kinds of measurements, Kogan cautions, “we cannot compare to earlier years, unfortunately.”

Yet other societal shifts have likely affected the trends that the ADDM has measured. Epidemiologists have speculated for years that increasing diagnoses of low-support autism, previously overlooked or diagnosed as something else, can explain much of the apparent epidemic. If that is true, then you might expect a shallower rise in cases of high-support autism. But data to test that possibility have been frustratingly lacking.

Durkin’s group has recently been trying to rectify that. Sifting through the ADDM dataset, they identified around 8,700 8-year-old

# THE INCREASE IN AUTISM PREVALENCE MAY NOT BE UNIFORM ACROSS THE SPECTRUM

BY JESSICA WRIGHT

*Both CDC research and a large European study suggest that severe functional impairment occurs in a shrinking proportion of the autistic community, as awareness of autism grows worldwide.*

The bulk of the increase in autism prevalence the United States between 2000 and 2012 can be attributed to children on the mild end of the spectrum.

The findings come from prevalence data gathered by the Autism and Developmental Disabilities Monitoring Network (ADDM) of the U.S. Centers for Disease Control and Prevention (CDC). Researchers presented the unpublished results today at the 2018 International Society for Autism Research annual meeting in Rotterdam, the Netherlands.

In a separate report, researchers also presented early estimates of autism's prevalence in Europe, based on surveys in 14 countries.

Estimates of autism's prevalence in the U.S. have risen significantly from 1 in 150 children in 2000, when the ADDM began tracking it, to 1 in 59 children for data collected in 2014. There are several theories about the reasons for this rise, but most experts agree that most of it is the result of increased awareness about the condition.

The new data support this theory, says Eric Fombonne, professor of psychiatry at Oregon Health and Science University in Portland, who was not involved in the study. The results suggest that autism prevalence is rising because the ADDM is detecting children now that it would have missed 18 years ago. "To me, it's an artifact of detection," he says.

The researchers looked at scores on the Vineland Adaptive Behavior Scales, a measure of daily functioning, for 12,739 children thought to have autism. (They had scores for 55.9 percent of children with autism identified by the ADDM between 2000 and 2012.)

The researchers used the scores to group children into four categories, ranging from those having no limitations in functioning to those with moderate-to-profound limitations.

The number of children with autism in this most severe group remained stable from 2000 to 2012, says Daisy Christensen, an epidemiologist at the CDC who presented the findings. Children who had no apparent limitations in functioning and those with borderline limitations made up the bulk of the increase.

## FIRST STEPS:

It is possible to make these comparisons because there are prevalence data for the U.S. that go back 20 years. By contrast, there have been no official prevalence reports for Europe—until now.

Researchers are wrapping up a concerted effort across 14 European countries, in response to an official request from the European Parliament, says Joaquín Fuentes, head of the child and adolescent psychiatry unit at Policlínica Gipuzkoa, a hospital in San Sebastián, Spain. On Wednesday, Fuentes presented data from Italy, Austria, Poland, Romania, Portugal and Spain, the countries for which the consortium has the most information to date.

Overall, the researchers found a prevalence between 0.6 and 1 percent across these six countries; prevalence in the U.S. is 1.69 percent. Roughly 0.7 percent of children in Spain have autism, according to the analysis.

"It's the largest study of its kind involving countries for which we have absolutely no sense of prevalence, so I think it's great," says Ami Klin, director of the Marcus Autism Center in Atlanta, who was not involved in the study.

The report covers 160,000 children enrolled in participating schools in the countries. The researchers gave teachers questionnaires to nominate children they suspected of having autism—based on whether the children are socially awkward or do not seem to understand others' feelings, for example.

For each nominated child, the researchers also selected three random children from the same school as controls. All these children then filled out the social communication questionnaire, an autism screen. Clinicians then evaluated all the children who scored above a cutoff for autism.

This article was originally published in 2018.

children for whom psychologists had assigned an adaptive behavior score—a rough proxy for the degree of functional limitations their autism causes. The higher the score, the less support the child needs. As it turns out, scores gradually increased for each successive cohort of children in the study from 2002 to 2014, Durkin and her colleagues reported in June 2020 at the INSAR conference. Among children with an autism diagnosis, the degree of functional impairments appeared to decline with every passing year.

LEARN MORE



<https://www.spectrumnews.org/news/new-u-s-data-show-similar-autism-prevalence-among-racial-groups/>

For further details on the cultural issues with autism screening tools, see “Is Autism Harder to Measure in Some Cultures Than in Others?” on page 140 and “Autism Diagnosis Rates Are High Among U.K. Students as Well” on page 76.

Along with this progress in recognizing less disabling forms of autism, the profession has made headway toward eliminating the pronounced racial disparities in rates of diagnosis seen in the U.S.—but few other countries—since ADDM measurements began. Until 2020, every ADDM survey showed higher rates of autism among whites than among Black, Hispanic and Asian children, even after adjusting for income. Prevalence is also generally higher among the rich than among the poor.

“The most parsimonious hypothesis is these are artifacts of known disparities in healthcare access and quality,” Durkin says. But in March 2020, the latest report from the ADDM showed the gap seems to have [finally closed among the races](#) in 2016. Diagnostic rates are still lower for Hispanic children, however, and Black children are diagnosed at older ages than white children are (see “Being ‘Autistic While Black’ Can Mean Waiting Longer for a Diagnosis,” page 118).

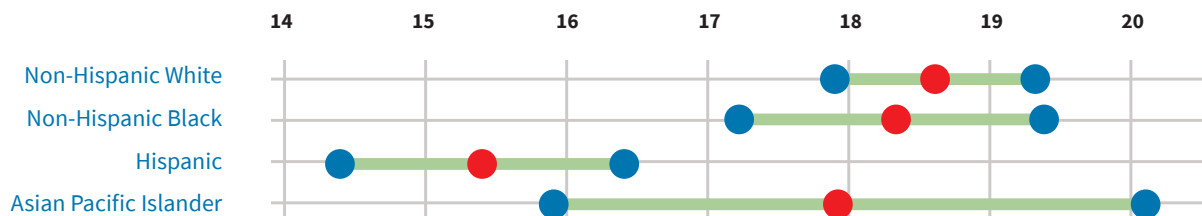
In the U.S., with its hodgepodge healthcare system, access to pediatricians and, in particular, to child psychiatrists also varies enormously from one city and state to the next. “We know that there’s a shortage of clinicians who are trained to diagnose developmental disabilities and autism,” Kogan says. Those shortages are more acute in some places than in others.

Such variations, as well as differences in education, income and insurance coverage, may explain in part the otherwise baffling range of prevalence numbers measured by the ADDM across its 11 sites. In the Denver metro area, for instance, 1.2 to 1.4 percent of 8-year-olds met the criteria for autism in 2016, the ADDM estimated. In New Jersey, by contrast, 3.0 to 3.3 percent did. While media outlets focused on the ‘total’ 1.8 to 1.9 percent prevalence the CDC reported, results from an astonishing nine of the 11 sites do not overlap at all with that confidence interval.



## PREVALENCE OF AUTISM AMONG 8-YEAR-OLDS, BY RACE (PER 1,000 CHILDREN)

The ADDM's studies found that autism prevalence in 2016 was about the same among Black, white, and Asian or Pacific Islander children in the U.S. But it was significantly lower for Hispanic children, suggesting that Hispanic children with autism were not being identified as often as other autistic children.



These are total prevalence rates across 11 Autism and Developmental Disabilities Monitoring Network sites. Blue dots represent 95 percent confidence intervals.

One other factor—though of unknown magnitude—generating hot spots of prevalence in places like California, New Jersey, Maryland and Northern Ireland could be the migration of families in search of better services for their autistic children. Debbie Lyons, a stay-at-home mom turned remodeling contractor, recounts how she and her husband decided to move from Florida to Madison, Wisconsin when their son Nicolas, then 3 years old, was diagnosed with autism. They chose it because there, Nicolas could get 35 hours a week of one-on-one therapy. When the state reduced those hours because of his age, they moved again—this time to Seattle. At age 13, Nicolas attended a special-needs class twice a week in a public middle school, which also gave him a communications device to use until he ‘graduated.’

Washington state offered few adult services for Nicolas to graduate into, so when he was 19, the family crossed the country once more and resettled in Maryland. There Nicolas joined a cohort of students his own age and, a couple years later, started an adult day program. Maryland’s services were good for her son, Lyons says, and the state also doubled the hours and increased the hourly wage that they pay her to care for him in lieu of hiring an outside caregiver.

“I wonder how many people move for their children with autism,” she says. “It’s a lot to move.”

But moving is a one-time exertion. If relocating means extra help every day in caring for a high-support child, that might be a trade-off some parents are willing to make.

# SYSTEMIC RACISM SHOWS UP IN AUTISM PREVALENCE STUDIES

BY JILL ADAMS

*Racial disparities undermine the quality of health care and access to an accurate and timely autism diagnosis.*

Estimates for autism's prevalence in three U.S. states reveal significant inequalities in how children of different races and ethnicities are counted and assessed, according to two studies published in 2019.

In Wisconsin and Colorado, Black and Hispanic children are more likely than white children to lack health or residency records, which excludes them from prevalence analyses, suggests a study published in *Autism*<sup>1</sup>. And in New Jersey, Black children are half as likely as white children to receive an autism assessment by age 3, according to work presented at a 2019 conference.

"We need to do more," says Maureen Durkin, lead investigator of the published study. "There are so many barriers to getting a full assessment."

The data for both studies come from the Autism and Developmental Disabilities Monitoring Network, a nationwide surveillance program run by the U.S. Centers for Disease Control and Prevention.

The program has consistently found racial and ethnic disparities in autism prevalence. Its researchers reported last year, for instance, that fewer Black children than white children have been diagnosed with autism in three states, including Wisconsin, and fewer Hispanic children have been diagnosed in seven states, including Colorado<sup>2</sup>.

In the new study, Durkin and her colleagues found the reasons for these discrepancies in state records. The study exposes systemic biases in children's access to expert care, says Sydney Pettygrove, assistant professor of epidemiology and biostatistics at the University of Arizona in Tucson, who was not involved in either study. "The way

our whole system sees and treats people is based on their ethnic group," she says.

Identifying the gaps is the first step to closing the gaps, other experts say.

"These data are really important," says David Mandell, director of the Penn Center for Mental Health at the University of Pennsylvania. "There is tremendous value in understanding how children get diagnosed, what their service experience is like, what disparities there are in services and how we can fix it."

## PATCHY PAPERWORK:

Durkin and her colleagues revisited the records that clinical reviewers had used to gauge autism prevalence in Wisconsin and Colorado.

The reviewers generally categorize children as 'autistic,' 'not autistic' or 'suspected case' based on the children's school and healthcare records. Children without healthcare records are more likely to fall into the suspected category than those with complete information, the study found. And the ultimate estimates for prevalence do not include these suspected cases.

Among children flagged for autism, 45 percent of Black children and 23 percent of Hispanic children lack healthcare records, compared with 11 percent of white children. And these Black and Hispanic children are significantly more likely than their white counterparts to be classified as a 'suspected' rather than 'confirmed' case of autism.

When the researchers added back a subset of suspected cases to their calculations for prevalence, the disparity between Black and white children disappeared. However, the difference between Hispanic and white children remained.

"It's the scantiness of the records that did explain the Black and white difference in prevalence," Durkin says.

Children with patchy residency records are also liable to be overlooked, Durkin says. For instance, any child who is missing proof of residency for the year she turned 8 is automatically excluded from the analysis. "It's a very stringent requirement," Durkin says.

This problem particularly affects Hispanic children: 44 percent of the children flagged as having autism but

missing residency information are Hispanic; by comparison, Hispanic people constitute 19 percent of total autism cases in Wisconsin and Colorado.

#### ASSESSMENT LAG:

The study adds to this picture of racial inequalities. It found that Black children in New Jersey are half as likely as white children to be evaluated for autism by age 3. This assessment gap exists despite the prevalence of autism being about the same across Black, Hispanic and white children in the state. And the disparity held even when the researchers controlled for sex, level of autism severity and socioeconomic status.

The discrepancy is important because children evaluated later often end up waiting longer to receive treatment, and timely treatment is among the best indicators of a good outcome for autistic children.

The large gap surprised the study's lead investigator, given New Jersey's reputation for equitable delivery of clinical and educational services. "I still don't understand it," says Walter Zahorodny, who directs the New Jersey autism study site at Rutgers New Jersey Medical School in Newark.

The difference between Hispanic and white children's ages at early evaluation was not significant after the researchers corrected for socioeconomic status and other factors. Zahorodny's team presented the findings at the 2019 meeting of the International Society for Autism Research in Montreal.

The new studies suggest that systemic biases affect both how researchers collect data to estimate prevalence and children's access to services.

Researchers are working to minimize these biases in data collection, Pettygrove says. "We are trying to whittle away what [prevalence] differences are not real but explainable."

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This article was originally published in 2019.

# 6

## Simple to Ask, Hard to Answer

*The confusing trends in autism prevalence start to make more sense when you understand the many sources of uncertainty that aren't captured in simple metrics like confidence intervals.*

By now, you've probably noticed a theme as we've looked at research into possible biological and sociological causes of the rise in autism prevalence: uncertainty is everywhere. It's inescapable to an extent that can baffle non-experts and even makes many researchers in this field uncomfortable. The question seems so simple: How many autistic people are there? And yet the major limitations of our diagnostic and statistical tools make it almost impossible to answer that question definitively.

So let's take a moment in this chapter to focus on some of the biggest sources of uncertainty in autism epidemiology, most of which aren't captured by the confidence intervals reported in papers.

The IHME in Seattle is renowned for finding clever ways to work around uncertainties and to account for them in their Global Burden of Disease project. But Theo Vos says that in the case of autism, his group is flummoxed by what he calls “a triple whammy”: noise in the data, complicated by shifting diagnostic methods, piled on top of hard-to-measure changes in the volume of parents seeking diagnoses for their children as awareness and insurance coverage grow. Because of the complex interactions of these variables, he says, “any sort of underlying trend [in the true prevalence of autism] would be really hard to detect.”

Confounding factors of these kinds also have complicated our

ability to accurately track trends in disorders of other kinds, such as diabetes, Vos adds. In the 1990s, he says, “you would find 50 percent of people that you are identifying with diabetes [in studies that actually tested their blood glucose levels] say ‘Oh no, I’ve never been told I have diabetes.’” In more recent surveys, he says, “maybe a third or a quarter of people have not been diagnosed previously.”

The dramatic rise in self-reported diabetes that shows up in NHIS figures thus comprises a true trend—increasing obesity-related diabetes—overlaid atop what he calls “a false trend” created by growing awareness, more common screening, and improvements in treatments that allow people to live longer with diabetes.

Despite the difficulties in disentangling all of those effects, the IHME has not hesitated to sound the alarm over obesity and diabetes as “a major public health epidemic that must be stopped.” In stark contrast, the GBD shows autism as virtually unchanging since 1990 in most countries.

When I visited Vos and Santomauro in 2019, I asked them about this. Why did their chart of autism prevalence in the U.S. show a perfectly horizontal line, locked at 1 percent, even though the cloud of data points feeding into their model—from dozens of studies such as those published by the ADDM—clearly drifts upward and to the right? They confessed that they had actually forced their model of autism prevalence to ignore any time trend in the data. “We do include the estimates,” from those studies, Santomauro explains, “but we adjust for potential bias, and we lock out any type of time trend that they might give.”

This bears repeating: the GBD, which health authorities worldwide use to monitor trends in diseases and disabilities, discounted the majority of autism prevalence studies and made assumptions that effectively suppressed any apparent trend in autism. They did that for the U.S., for Northern Ireland, indeed for most countries.

Why? In short, they told me, autism is mostly measured using unreliable methods. Aside from the 1998 Brick Township study, Santomauro explained, only one other U.S. study on autism had met GBD criteria for reliable prevalence measurement. None of the ‘official’ numbers—not any of those five estimates published by the U.S. government—make the cut. So the IHME essentially discards them

*It’s hard to know how much to trust the results from the CDC’s ADDM network, Fombonne and Santomauro say, because only one independent study has tried to validate the ADDM approach, and it was imperfect and done more than a decade ago, before the big shifts in the diagnostic criteria for autism.*

as interesting guesses. (In a 2020 update, the IHME adjusted its model in ways that permitted a small increase in U.S. prevalence after 2005. But as of 2021, their estimate of 0.53 percent to 0.76 percent was still far lower than those from other research groups.)

Fombonne echoes many of the same reservations that the IHME experts have. Those start with the absence of an objective diagnostic test that can be widely applied in large studies that represent the population as a whole. The testing criteria for diabetes may have shifted over the years, but they are based on standard blood tests that are reliable and easy to perform.

Santomauro says that developing an objective and stable standard for diagnosing autism should be a top research priority. But Fombonne says that it's hard to imagine a test for autism, spanning as it does such a wide range of behavioral manifestations, that would take relatively little training to administer accurately and consistently.

A similar problem vexed epidemiologists trying to measure the prevalence and consequences of obesity, recalls Katherine Flegal, who retired in 2016 from the CDC's National Center for Health Statistics after decades working on national studies of obesity. A breakthrough happened, she says, when experts finally settled on the objective definition of obesity as a body-mass index of 30 or higher. It took years of consensus building to arrive at that criterion—an imperfect but simple test that any healthcare worker can perform—but that achievement made it possible to do meta-analyses and international comparative studies that paid huge dividends in understanding the causes and consequences of the condition.

The opposite happened with autism, Fombonne recalls, as experts tried to divide the spectrum into subtypes based on constellations of traits and their



severity. That effort backfired, he says. Behaviors of real people don't divide along such neat lines, and clinicians were not able to reliably and consistently assign subtype diagnoses. With the DSM-5, the field has backtracked, consolidating Asperger syndrome and other subtypes into a single diagnosis: autism spectrum disorder. While that may be progress of a kind, it has thrown a wrench into long-term studies like those from the ADDM.

And the ADDM has deeper problems as well, Fombonne and Santomauro say. The 11 sites in the ADDM network vary greatly in size, and the demographics of their participants don't allow results to be extrapolated to the U.S. population as a whole. Even more worrisome, Fombonne and Santomauro complain, is that the CDC uses an unusual technique for classifying children as autistic—a method that has not been well validated.

ADDM researchers never examine the children in their study in person, nor do they rely on evaluations made by physicians, though they certainly take those into account. Instead, ADDM experts read through selected medical records on each child—and, at some of the sites, school records as well—and then make their best guess as to whether the child is on the spectrum.

There is a good explanation for this seemingly odd approach, as Durkin explained in Chapter 2. In order to include all children who live in the study areas, the ADDM sites operate as public-health authorities doing community surveillance—similar to how public-health departments now monitor COVID-19 test results. Because they never asked for the informed consent of the participants, they cannot contact families to arrange the clinical evaluations that would be needed to check whether their diagnostic 'calls' are actually correct.

Needless to say, doing that would also be hugely labor-intensive and quite expensive.

The unfortunate consequence, both Fombonne and Santomauro say, is that it's difficult to know how much to trust the results published by the ADDM. They point out that only one independent study has tried to validate the ADDM approach, and it was imperfect and done more than a decade ago, before the big shifts in the DSM-5's diagnostic criteria. A second study frequently cited in ADDM papers as validation evaluated only the consistency of the ADDM estimates, not their accuracy, Fombonne says.

The single validation trial, performed by CDC researchers, used clinical exams of 177 of the 8-year-olds involved in the ADDM study at the Atlanta site to determine how accurate the ADDM researchers were in identifying children with autism. They concluded that the ADDM's classifications for those children were correct 66 to 93 percent of the time. But in reaching that conclusion, the researchers had to overlook some major problems with participation in the validation trial. Nearly two-thirds of the children they wanted to examine were unreachable or deemed ineligible due to language or geographic barriers. And of those families contacted, more than half refused to cooperate.

Problems like this occur all the time in autism surveillance studies, Fombonne says, and they introduce a potentially serious kind of error known as participation bias. In the landmark study he worked on in South Korea, for example, "we assumed that those who participated are the same as those who did not participate. And this is a huge assumption," he says, seeing as just 63 percent of the children in the study area participated.

"There were so little services, so much stigma, that probably the families who came to the assess-

ments were more likely to have a child with a problem, and they wanted answers.” This phenomenon may well have biased the study group to make autism appear more common than it actually was, as Fombonne and his coauthors acknowledged in their 2011 paper.

Santomauro says he suspects that ADDM estimates now significantly overstate the prevalence of autism—but that, too, is a guess. Until a new and better validation study is conducted, such criticisms will continue to undermine some researchers’ confidence in the ADDM numbers.

In addition to participation bias, the NSCH and NHIS results are affected by other sources of uncertainty, Kogan acknowledges. One issue with the NSCH is that it relies on the recollections of parents, who are not always the most reliable reporters. Kogan points to other studies that compared parent reports to clinical records and found the former to be at least 93 percent accurate. But the 2007 survey added a follow-up question for parents who said their child had been diagnosed with autism. In response, “38 percent of those parents said, ‘No, my

child doesn’t currently have the condition,’” Kogan reports. “We were floored by that number,” he says, because autism is considered a lifelong condition. Perhaps due to refinements in wording or to growing awareness of what autism is, the number of ‘lost diagnoses’ has since declined to 7 percent, he says.

To all these uncertainties about what the true prevalence of autism is, we have to add one more giant source of ignorance: the near impossibility of establishing what the actual prevalence of autism was, decades ago when autism in so many children was overlooked. Those children are now adults, and if there were a way to accurately measure autism in 30-, 40- and 50-year-olds, that could give us an answer to the question of whether autism is really far more common now than it used to be.

But diagnosing autism in adults is even harder than it is in children, Fombonne says. “There are no psychometrically validated tests” for doing so, Patricia Dietz of the CDC and her colleagues wrote in May 2020 in a study that attempted, by way of large assumptions, to estimate the number of autistic adults in the U.S. Few other studies have even tried.



# The Johnny Appleseed of Autism Prevalence Research

BY JESSICA WRIGHT

*After decades designing autism prevalence studies around the world, Eric Fombonne considers their flaws and suggests some ways to do better.*

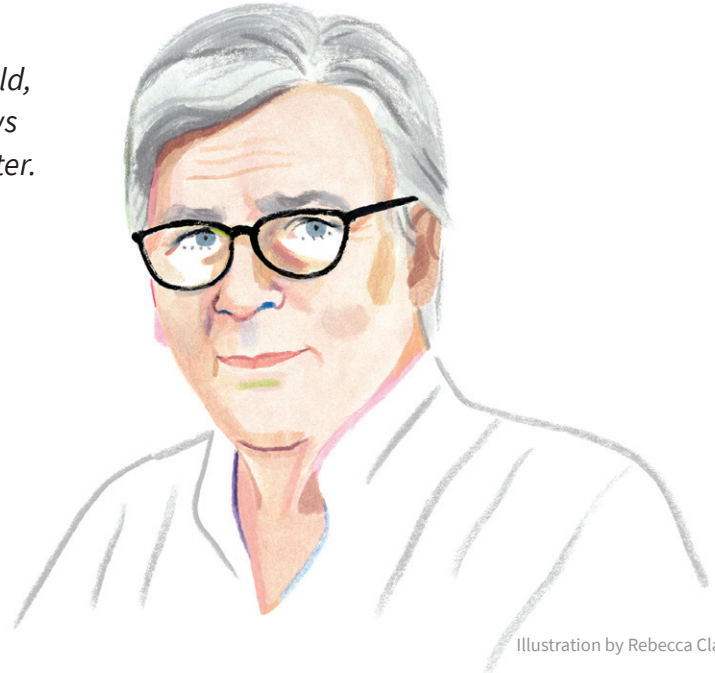


Illustration by Rebecca Clarke

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The lore about autism is that prevalence rates are rising—leading many people to call it, misleadingly, an ‘epidemic.’ Even among scientists, many assume that the largest prevalence estimates are the most accurate.

But epidemiologists know that the prevalence depends greatly on the methods used in the study.

In 2018, for example, the National Health Interview Survey in the United States reported an autism prevalence of 2.76 percent in 2016, up slightly from 2.24 percent in 2014. However, a 2014 survey of 8-year-olds by the U.S. Centers for Disease Control and Prevention (CDC) reported a lower prevalence, at 1.69 percent. And preliminary data from a 2012 survey of 8-year-olds in South Carolina suggested a higher estimate: 3.6 percent.

What may not be obvious is that these studies varied greatly in their design, which contributed to the varying estimates of prevalence<sup>1</sup>, says Eric Fombonne, professor of pediatrics at Oregon Health and Science University.

We asked Fombonne about how a study's design influences prevalence—and in many cases, inflates the estimates.

**SPECTRUM:** *Are studies of autism prevalence beginning to approach the true levels?*

**ERIC FOMBONNE:** We don't know what the true autism prevalence is. In the past 5 to 10 years, the authors of studies finding high rates of autism have had the tendency to be a bit blind to the problems in their own studies. I'm concerned about the lack of critical appraisal in what we do.

**S:** *How might a study overestimate autism prevalence?*

**EF:** One study I participated in looked across all schoolchildren in one region in South Korea by sending questionnaires to all teachers and parents in the region. Of these children, those who scored above a cutoff for autism were invited to have a clinical confirmation of their diagnosis.

But only some of the parents responded to the screening questionnaire, and then only some of the parents of the children invited for an evaluation agreed to bring in their children. Still, to calculate the prevalence, we had to make the audacious assumption that the children whose families participated are as likely to have autism as those who didn't.

When we started the study, there were few services for autistic children in Korea. So parents of a child with autistic features might have been seeking a diagnosis for the child—and might therefore have been more likely to participate in our study than parents of typically developing children. If that were true, the autism prevalence we obtained (2.64

percent) is likely to be an overestimate.

An unpublished study of autism rates in South Carolina based on the same design, with similarly low participation rates, makes comparable unchecked assumptions. So I worry that its high prevalence could be an overestimate as well.

**S:** *Do the CDC prevalence studies make similar assumptions?*

**EF:** No, the CDC does not attempt to assess everybody in a population. Instead, it looks in the medical and special education records of each child in a certain region to determine whether a child meets criteria for its surveillance definition of autism. Children with no relevant notations of social problems in their records are assumed not to have autism. This method is not subject to a bias from parent responses, although other types of bias are possible.

Still, it is not clear how accurate the CDC's surveillance criteria for autism are. In a study designed to validate these, researchers found that between 20 and 40 percent of children who met the CDC definition of autism did not actually have autism, so the CDC rates could be overestimates<sup>2</sup>.

**S:** *Are there any other problems with the CDC studies?*

**EF:** Yes. One important flaw in the CDC criteria is the inclusion of pervasive developmental disorder not otherwise specified (PDD-NOS). PDD-NOS is an ill-defined category in an outdated version of the psychiatric manual the Diagnostic and Statistical Manual of Mental Disorders. It may be loosely applied to children who do not meet full requirements for autism. The most recent CDC report

doesn't specify who has PDD-NOS, but in previous CDC studies, roughly 40 percent of the CDC 'autism' cases were in fact PDD-NOS.

Another issue is that of every 100 children the CDC researchers determine to have autism, only 80 have a reference to autism specifically in their medical or school records. So, one in five 8-year-old children the CDC decides has autism had never been picked up as autistic by any professional. At age 8, how is this likely? This proportion has remained unchanged in CDC surveys, despite a steady increase in autism awareness over the past 15 years. It is unfortunate that we cannot perform a direct in-depth investigation of these children.

**S:** *Are some children inaccurately diagnosed with autism in real life?*

**EF:** Yes. I led a team that verified autism diagnoses prior to inclusion in a neuroimaging study. Trained researchers performed independent state-of-the-art assessments of over 200 children with an existing autism diagnosis. At least 30 percent of these children turned out to not have autism. It was mind-boggling. Some clinicians appear to diagnose autism in children who don't have it simply because there are more support services available for children with autism than for children with other complex behavioral conditions.

I wonder about the long-term impact of misclassifying these children. It was disheartening to see so many children and teens who don't have autism carrying a label of 'autism' at school and in their homes.

In my clinics 25 years ago, I remember explaining to parents who had no clue about autism why their child qualified for the diagnosis. Things have now reversed. Nowadays, some parents and pro-

professionals push for that diagnosis and resist a 'not autism' conclusion because it may come with less support.

**S:** *Do you think some methods are better than others for estimating prevalence?*

**EF:** Not really. There is no standardized way to do these studies. Each study has its unique strengths and limitations, and there is no quick fix to this problem. However, I see two ways to improve this area of research. One would be to add a longitudinal component to prevalence surveys, which so far provide only a static picture. Focusing on trajectories would better capture essential features of autism. Second, epidemiological studies will get better when biomarkers become available. These biological measures should reduce the infernal noise in our current autism assessments, which rely on behavior.

Meanwhile, we need to look carefully at each study we conduct and consider potential problems with its methodology. I worry that investigators are pressured to confirm high prevalence rates. I also worry that uncritical faith in diagnostic criteria and standardized instruments might lead researchers to disregard the profound measurement issues that persist in our field.

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# 7

## A Trend That Must End

*Several unusually informative studies shed light on the question of how high measured prevalence may eventually rise. But it may be unrealistic to hold out hope of a truly accurate number.*

Some of the methodological mountains mapped in the last chapter, such as the inaccuracy of screening tools, may be insurmountable. Fombonne may be the ‘Johnny Appleseed’ of the field, consulting on autism-screening studies around the world, but each one has left him frustrated. “There is no narrow way to do it. Because autism is a relatively rare condition,” he says. And measurement of any rare condition involves a fundamental trade-off: “If you are too stringent, you lose sensitivity,” he says. “If you are too lax, you pay a price in false positives.”

But science could better approximate reality by concentrating funding and brainpower on larger studies that are more rigorous in their design and analysis, research suggests.

Large community surveys, especially those that look at both adults and children and involve participants who are representative of the general public as a whole, could produce a leap in understanding, Santomauro, Fombonne and others say. The key, Fombonne says, is “active case-finding”: looking for people with autism not just in schools, not just in workplaces, but also in group homes, on street corners and in the hidden parts of society.

Terry Brugha, a psychiatric epidemiologist at the University of Leicester in the U.K., and his colleagues showed the power of this approach. They sent interviewers to more than 14,000 randomly selected addresses in a central region of England to administer an autism questionnaire to adults living there. From those who screened positive, they then clinically evaluated a subset that they selected to be representative of the population at large.

To the surprise of many in the field, Brugha and his colleagues reported in 2011 that autism affects about 1 percent of English adults—in line with the prevalence then measured in English children. “We have demonstrated for the first time in the general population that the rate of [autism] is not significantly associated with age, suggesting that the causes of autism are temporally constant,” they wrote.

Finding that the prevalence among adults is just as high as it is among children calls into question the notion that any sort of ‘epidemic’ is underway. The notion that autism is actually no more common now than decades ago might seem implausible to many outside the field. But, Durkin says, “I think it could be true” that a large fraction of autistic adults were missed and never received a diagnosis. “It makes total sense.”

A follow-up study in 2016 that drew on a national registry of people with intellectual disability confirmed the finding. “The picture that emerges,” Brugha and colleagues argued, “is of a large population of adults who are significantly disabled whose needs remain unmet because they are not recognized, particularly when they do not have intellectual disabilities.” They urged researchers in other countries to replicate this kind of study. As of the end of 2020, however, no others had been published.

Epidemic or no, the accelerating pace of diagnosis among children begs the question of where this trend will end. Trees do not grow to the sky, and obviously we do not all have autism, so at some point the rising prevalence among children will flatten and may then dip. But when, and at what level?

Prevalence among adults seems likely to continue rising for another generation or two, experts say, as the higher numbers of children recently recognized to have autism mature. No country has yet reported a statistically significant decrease in prevalence. And in some places, such as Belfast, Northern Ireland, the reported prevalence of autism has shot through 7 percent and continued to rise.

But two clever studies offer some foresight, having tracked the accumulation of diagnoses among groups of children all born in the same year—so-called birth cohorts. One remarkable study in Denmark, published in 2018, collected records on every diagnosis of autism made for the 2,055,928 people born in the country between

1980 and 2012. By examining medical records through 2016, a team of researchers was able to track the age at which each autistic child in 17 successive birth cohorts received their diagnosis—including a surprising number who were diagnosed only after becoming adults.

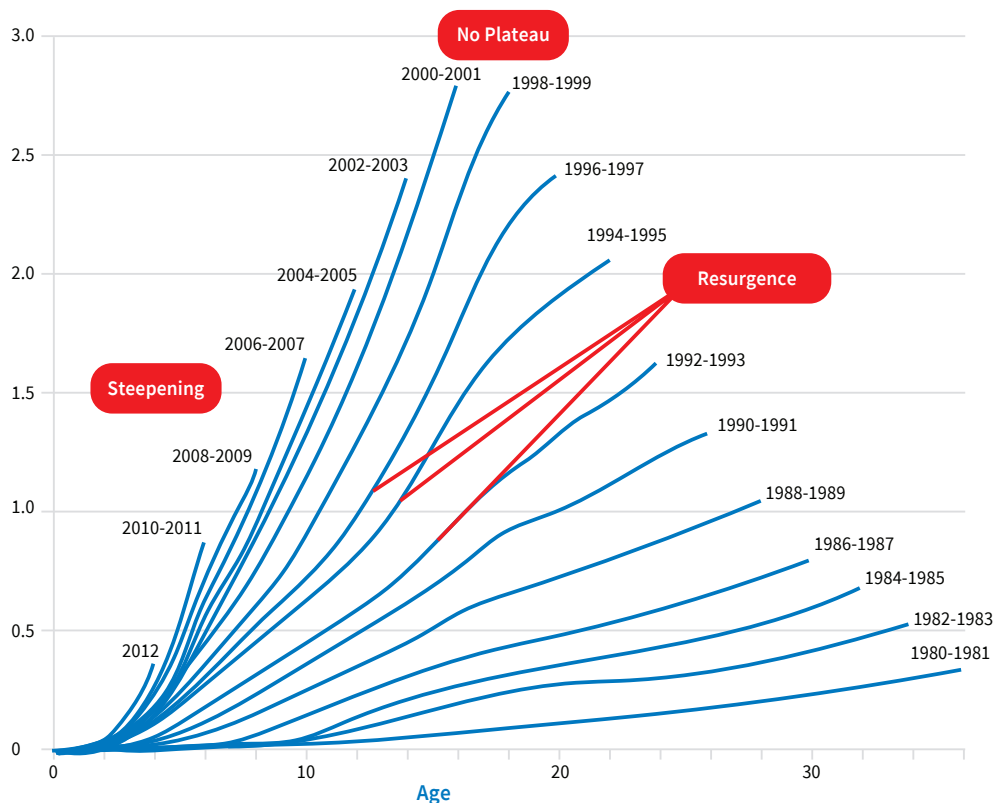
The fan-shaped graph plotting the diagnostic trajectories of these groups tells a remarkable story (see chart at right and “In the Most Comprehensive National Study So Far, Autism Grows to the Sky,” page 62). Each curve should take on an S shape, as most children with autism are diagnosed a few years before or after beginning school and then diagnoses taper off. And for Danes born from 1988 to 1996, that pattern appears. But among those born before 1986, few were diagnosed before age 10. And even more surprising, the pace of diagnosis accelerated during their adolescence—perhaps not coincidentally, right around 2008 for each cohort, which was shortly after screening started becoming standard pediatric practice.

Equally interesting, as of 2016 the curves for children born in the 2000s still showed no hint of a plateau. Even at age 16, the group born in 2000 continued to add autism diagnoses at a fast clip, suggesting that measured prevalence for that and successive cohorts will ultimately exceed 3 percent or more.

Meanwhile, a possible plateau in autism prevalence could be on the horizon in the U.S., according to a 2018 study by researchers at the Geisinger Autism & Developmental Medicine Institute, the Mayo Clinic and Baylor College of Medicine. The research draws on a unique dataset, known as the Rochester Epidemiology Project. This project incorporated the Mayo Clinic’s huge database of medical records collected since 1907 for every person in Olmsted County, Minnesota, who receives care at any of the doctor’s offices, hospitals, labs or other facilities there. Nearly 90 percent white and documented to the hilt, the highly homogeneous county is a gold mine for answering epidemiological questions for which racial and ethnic diversity complicate rather than clarify the situation.

Panning through this rich, decades-long dataset, the researchers analyzed medical charts, as well as records from all public and private schools, for all 31,220 children who were born between 1976 and 2000 to mothers residing in the county and who were still living there at age 3. Using techniques similar to the ADDM’s, experts examined

## CUMULATIVE INCIDENCE OF AUTISM IN DENMARK, BY BIRTH COHORT (PERCENT)



Exploiting Denmark’s vast national health registry, researchers there were able to reconstruct the diagnostic history of essentially every person confirmed to have autism in that country since the 1980s. They then grouped all of those people into two-year birth cohorts: All those born in either 1980 or 1981, for example, are included in the 1980-81 cohort and were 35 or 36 years old in 2016, when this analysis was performed. Plotting the increasing count of autism diagnoses in each cohort by age in this way reveals a number of intriguing insights:

**STEEPENING:** In each successive birth cohort, without exception, autism diagnoses have accumulated at a quicker pace. That shows that children have been identified as autistic at younger and younger ages as awareness has grown and screening has become increasingly routine.

**NO PLATEAU:** Autism is a lifelong condition, so we should hope that everyone who is on the spectrum will receive a diagnosis well before they reach adulthood. The cumulative incidence curve would then go horizontal. Instead, these data show that, even in a rich country that has universal healthcare, adults in their 20s and 30s are continuing to be diagnosed for the first time. What’s more, the prevalence for teenagers looks set to easily exceed 3 percent. There is no hint in this trend of where the prevalence will eventually top out for those born in the 2000s.

**RESURGENCE:** A watershed moment in autism diagnosis happened in 2007, when the American Academy of Pediatrics recommended universal screening, and doctors around the world took note. The effect of that uptick in screening is visible here as upward inflection points in the curves at ages corresponding to the years 2008 to 2010, suggesting that many doctors gave even their preteen and teenage patients a fresh look.

# IN COMPREHENSIVE NATIONAL STUDY SO FAR, AUTISM PREVALENCE CONTINUES UPWARD CLIMB

BY ALLA KATSNELSON

*The results show no hint of a plateau in prevalence rates as of 2016.*

The rising prevalence of autism shows no sign of leveling off, according to a 2018 study that accounts for every diagnosis made in Denmark over 32 years<sup>1</sup>.

That may be in part because more adolescents and adults are being diagnosed with the condition than before, the researchers report. The results were published in *JAMA*.

“We don’t see any evidence that the prevalence increase is plateauing or stabilizing,” says Diana Schendel, professor of psychiatric epidemiology at Aarhus University in Denmark, who led the work. The findings highlight the need to expand support and services for adults with the condition, she says.

The study found an autism prevalence of 1.65 percent in 10-year-olds in Denmark in 2016. This broadly matches estimates from studies in the United States. However, the researchers tracked people into adulthood and found that autism prevalence seems to increase with age.

“This may be one of the first, if not the first, times that we’ve actually followed persons into adulthood” in a large-scale study to estimate prevalence at different ages, Schendel says. “I think the greater recognition of autism is catching up to these older individuals.”

Some experts question whether the prevalence in adulthood is as high as the study claims, however; that estimate seems much higher than what clinicians see, they say.

## RISING RATES:

Schendel’s team mined the Danish national psychiatric and patient registries for every autism diagnosis in people

born from 1980 to 2012; they followed these individuals through 2016. During this period, 2,055,928 people were born in Denmark, 31,961 of whom received an autism diagnosis.

Time-lapse data such as these reflect how estimates of autism prevalence change over time, says Eric Fombonne, professor of pediatrics at Oregon Health and Science University in Portland, who was not involved in the study. “It really shows that there is an increase in successive birth cohorts,” he says. “In that sense, it’s very welcome.”

However, the definition of autism and the way the condition is diagnosed have changed over the past few decades, and that might explain at least part of the increase, he says.

The study found the highest prevalence in people born from 2000 to 2001; 2.8 percent of this group had an autism diagnosis by 2016—3.89 percent of boys and 1.66 percent of girls. Autism prevalence at any given age went up year after year.

“These data offer a clear call that preparation is needed to address the significant and unique support needs among the emerging young adults with [autism],” says Catherine Rice, director of the Emory Autism Center in Atlanta, Georgia, who was not involved in the work.

## CAUTIOUS CALCULATIONS:

Yet some researchers are unsure what to make of the surge of diagnoses observed beyond childhood.

For example, about 0.5 percent of people born in Denmark from 1990 to 1991 received an autism diagnosis by 10 years of age, Fombonne says. But by the time these individuals are 26, the prevalence jumps to about 1.3 percent. This suggests that almost twice as many diagnoses are made between the ages of 10 and 26 as they are before age 10.

“I am suspicious of the validity of the diagnoses at later ages,” Fombonne says. “I don’t know what’s happening, but something doesn’t sound right.”

Confirming adult diagnoses with a clinical evaluation would help, he says. “Until we have that kind of data, we cannot be sure what is in there.”



Other experts share this concern. “I personally think we need to be very careful about first diagnoses in adulthood,” says Catherine Lord, distinguished professor in residence of psychiatry and education at the University of California, Los Angeles.

Fombonne is also perplexed by the sex ratio—2.3 boys to every girl—in the study compared with the usual 4-to-1 ratio.

“We also noticed this,” Schendel says. A closer look at the data suggests that the sex difference is wider at younger ages but narrows in adolescence. “Unless you have a follow up across these different ages, you won’t see that pattern,” she says.

Registry studies such as this one are attractive because they represent large populations, but they can have flaws.

For example, Lord says, once someone is diagnosed, his status in the registry is unlikely to change. However, work from Lord’s group shows that about 9 percent of people diagnosed as children shed their diagnosis by young adulthood.

Still, Lord says, the researchers are right that epidemiological studies rarely include people diagnosed as adults.

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This article was originally published in 2018.

records through 2015 to track both whether and when children showed evidence sufficient to warrant an autism diagnosis. Crucially, however, they applied the same diagnostic criteria across the entire, 39-year dataset—thus eliminating that major confounding effect of shifting definitions of autism

prevalence might be”—at least in that particular population. Santomauro says the methods the Mayo team used show great promise, “but I want to see more case-validation studies,” in which autism experts examine the children to confirm whether they are being categorized correctly as autistic or not.

*A recent study at the Mayo Clinic hints that the measured prevalence, at around 2.1 to 2.7 percent, is now near its true value, at least for the spectrum as it is currently defined and diagnosed.*

over time. For comparison, they also collected records on clinical diagnoses that the study participants had received from psychiatrists on their own.

As in the Danish study, the Mayo team plotted the cumulative incidence of autism by birth cohort (see charts on next page). Among 8-year-olds, the pace of diagnoses increased steadily throughout the late 1980s and 1990s. While increased awareness of autism and identification of symptoms no doubt account for much of that rise, “we cannot exclude the possibility of a secular increase in incidence prior to 1998,” the researchers wrote.

But then the data show a plateau in evident autism between 1998 and 2004 that they write “is not consistent with a true secular increase in [autism] during that period.” Nevertheless, clinical diagnoses continued to accelerate. The gradual convergence of the two curves suggests that pediatricians have been catching up, missing fewer autism cases with each passing year. If so, it could be that the measured prevalence, at around 2.1 to 2.7 percent, is now near its true value, at least for the spectrum as it is currently defined and diagnosed.

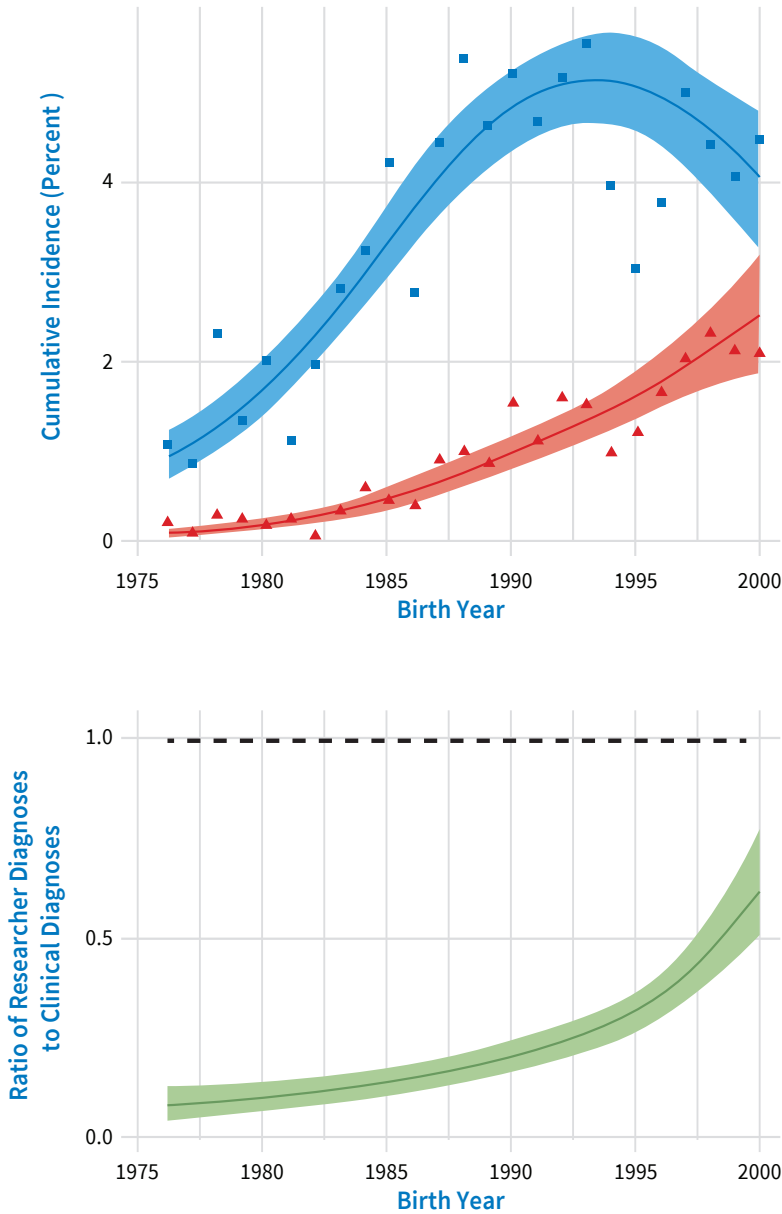
“It’s a treasure, Olmsted County,” Durkin says. “It’s possible this is a really good indication of what true

Validation studies involve lengthy appointments with highly paid experts who are in short supply, making them expensive to do at scale. Emerging automated diagnostics that run on smartphones, tablets or wearable devices and exploit new techniques in artificial intelligence might eventually help to bring down the cost of a reliable test (see “Can AI Deliver a Faster Path to an Autism Diagnosis?” on page 67).

If so, they may also reduce disparities in diagnostic rates among social groups, lower the age of diagnosis, catch the 40 percent or so of young children in the U.S. whose pediatricians currently fail to test them, and ease the long wait that parents in many places face to have their children evaluated and placed into early-intervention programs.

It’s also possible, however, that true prevalence will never be measurable. And we should be okay with that. As long as false diagnoses don’t become so common that they interfere with delivery of services to those who need them, a growing awareness of the prevalence of autism helps society accommodate the many people living with it.

After the Qatar study Fombonne and Shih worked on revealed, to the shock of many there,



Hints that doctors may at last be identifying nearly all autistic children appear in these two charts from a study done in 2018 at the Mayo Clinic. The scientists pored through their nearly complete collection of medical and school records on the residents of Olmstead County, Minnesota to independently identify those on the spectrum. They found that the prevalence of autism shot up from the late 1970s to the mid 1990s but then seemed to have reached a plateau at around 5 percent (*blue curve*) and may have even begun to decline. The fraction of children receiving a clinical diagnosis continued to rise through 2000, meanwhile (*red curve*). As a result, the ratio of the two, (*green curve*), looks on track to reach 1.0—the ideal value, corresponding to perfect diagnosis—but might overshoot it, due to overdiagnoses.

*It's also possible that true prevalence will never be measurable. And we should be okay with that. As long as false diagnoses don't get out of hand, growing awareness of the prevalence of autism helps society accommodate the people living with it.*

that more than 1 percent of children in the country have autism, the government set about “deliberately transforming the public policy landscape in that country,” Shih says.

Santomauro, too, testifies to the importance of growing awareness, drawing not on his research but personal experience. When he was diagnosed in 1995 at age five, “the doctor said, you know, ‘he’s got Asperger syndrome. It’s one in 10,000 people. And because of that he will never get a job. He will never move out. And he’ll never get married.’”

We’ve come a long way since then, yet there’s still far to go. From braille on elevators to ramped curbs and automatic doors, to assistive hearing devices in theaters, to warnings about stroboscopic flashes on TV shows, to gluten-free menus, allergen food labels and peanut-free flights, society has gradually modified public spaces and shared social and work experiences to enable those with disabilities to participate more fully and to contribute to our culture and economy.

Too few accommodations are yet made for those with autism. Better estimates and increased recognition of how prevalent the condition is could have a real upside, boosting the ability of ordinary people to understand how to interact with autistic children and adults in ways that are helpful and productive. Whether the true number is 7 percent, 3 percent or 1 percent, it’s virtually certain that we all have autistic relatives, classmates, coworkers and friends—who need our recognition and support.

# Can AI Deliver a Faster Path to an Autism Diagnosis?

BY LAURA DATTARO

*Algorithms may eventually be able to identify autistic people by analyzing data from wearable sensors and video cameras.*

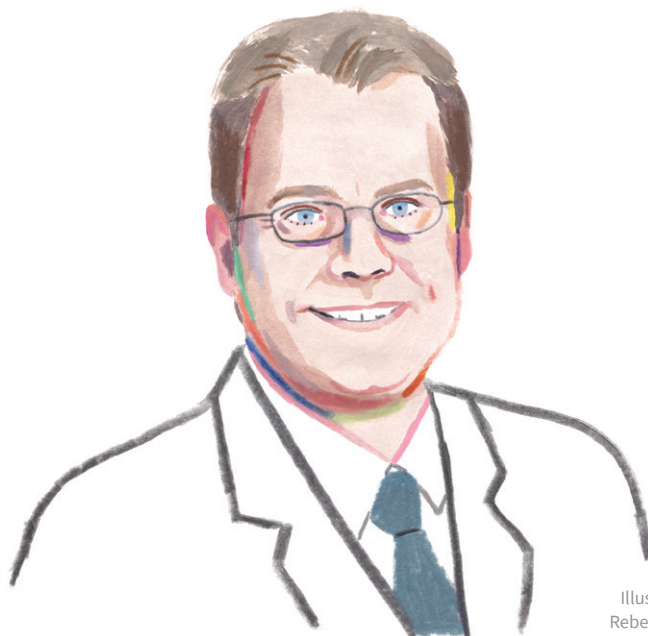


Illustration by Rebecca Clarke

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In 2015, Robert Schultz walked into his student's office to watch an animation of a talking dog. On a split screen, the cartoon dog made facial expressions that mirrored the student's own. Schultz had a flash of inspiration. He realized the software tools the student had used to take fine-grained measurements of his own expressions and superimpose them on the dog might also be used to diagnose autism: Whereas typical people unconsciously mimic the expressions of conversational partners, autistic people often do not.

Since then, Schultz, director of the Center for Autism Research at the Children's Hospital of Philadelphia in Pennsylvania, has created a video-camera system that simultaneously records 360 facial signals—such as how the corner of the mouth moves—exchanged between two conversation partners. Algorithms analyze how much these signals are coordinated and calculate the chance that one of the partners has autism. In a preliminary study, the system identified autistic people with about 90 percent accuracy.

Schultz spoke to *Spectrum* about how wearable sensors, cameras and microphones can fill gaps in autism research.

**SPECTRUM:** *Why did you get into the area of wearable technology for autism?*

**ROBERT SCHULTZ:** I've been in the field long enough that I'm frustrated. It stems from a dissatisfaction with current measurements of social functioning among individuals with autism. Why we have that dissatisfaction is a deeper question yet: It is the fact that autism is heterogenous. It doesn't seem to conform to a distinct category. It has amorphous boundaries; and it has lots of comorbidities.

When the light bulb regarding wearables went on one day five years ago, I thought, "This is going to be a huge benefit to the field, and I don't know why others don't see it." Now many people do.

I have done neuroimaging research my entire career, and still do, but in terms of what is most needed in the field now, I think it pales in comparison to the importance of digital phenotyping. We have a lot of granular data in science about brain function and genetics, but behavioral data lacks that kind of precision.

I think of wearables as a component under a rubric of digital phenotyping. The purpose is to digitally measure people. Wearables are one part of that solution because they can provide that granular data we need.

**S:** *What challenges in the field can be addressed with wearables?*

**RS:** There are a lot of deep theoretical questions and important research questions that promote our movement toward other ways of measuring behavior. For example, if you want really large samples, a traditional study running in my lab and many other labs might have a family, a parent with a child

or adolescent, or an adult in the lab for as long as seven hours. How do you scale that up to 1,000 or 2,000 individuals? Realistically, you can't, at least not with current funding models.

We're always left with a collection of studies that are, at some level, not satisfying. There are issues with replication and differing answers to similar questions. There's always doubt as to what those findings really mean. It's hardly the best foundation for developing a science of a neurodevelopmental condition. I think the question of wearables is fundamentally tied to these deeper questions. It allows us to take many more measurements more easily on larger samples.

**S:** *How can wearable technology be used to facilitate larger, more robust studies?*

**RS:** If you had a wearable and it was collecting data periodically or continuously in the wild, you would get a lot of data, essentially for free. It will be highly granular for whatever it's designed to measure. These signals are time series of data that readily lend themselves to analysis. By contrast, in a lab we collect less granular data, and it may have to be entered in a database, or there may be interpretation of data, first.

Questionnaires, which are so often used in research, are really the psychology of opinion. If you give me a questionnaire, it's my opinion about that child and this and that attribute. Or if I'm a clinician doing a diagnostic evaluation, I generally have to take all my impressions and summarize them into a score. Wearables give you the raw stuff of behavior. They can help form the foundation for a proper behavioral science.

**S:** *How are wearables and other technology useful in identifying autism?*

**RS:** When you think about autism, it has two fundamental diagnostic criteria. The first is inherently dyadic, when you're looking social issues. Social issues exist in a context—they exist with other people. Tools such as questionnaires don't directly acquire data on social behavior in a social context. So we're big believers in having assessments of two people interacting to help us understand the social deficits, and measuring these interactions with algorithms.

In our work to date, we find in a three-minute conversation, we can be about 90 percent accurate about whether a conversational partner has autism or not, just from looking at how well they coordinate behaviors with the person they're talking to. It also predicts dimensions, like the social score on the Autism Diagnostic Observation Schedule. We asked a group of experts—clinicians who do autism diagnoses—watching the same three-minute video whether the person of focus had autism. They were only about 80 percent accurate.

We have a National Institutes of Health grant now trying to move the age of initial diagnosis down to 1 year of age. The core symptoms as described in the Diagnostic and Statistical Manual of Mental Disorders aren't evident in any clear way at 1 year of age, so research still needs to discover the earliest emerging behaviors. These more granular features of the child's coordination of behavior with someone else are evident, and we can measure them.

**S:** *Is the technology useful in other areas of autism research?*

**RS:** I think wearables are going to be really important day to day as care-management tools. In terms

of turning them into therapies, if I'm doing something, a behavior, and I'm in the real world, and I can get feedback on what that behavior is or what a change in behavior is from someone else in real time, that could be used in a novel therapy.

In clinical trials of medications, there is also a lot of energy and excitement about using digital quantitative phenotyping as a more robust way to find a signal. Presuming that the medication is effective, how do you prove that it's effective without a many-millions-of-dollars treatment study, where you need hundreds and hundreds of people to pick up these signals? How long is it going to be before I see a signal? Are my measurement tools robust to repeated use? That is a very expensive proposition with traditional approaches. It becomes much cheaper and much more granular with a digital measurement.

**S:** *Where do you think the field of wearables is headed?*

**RS:** I am not so sure that the wearables we have now, such as accelerometers or gyroscopes, are the ones that are going to paint a detailed picture of a person. There are yet-to-be-invented wearables that I think would be better. I really think the thing we want for measuring behavior is a microphone and a camera, which could be made wearable. Because with that, you can capture everything.

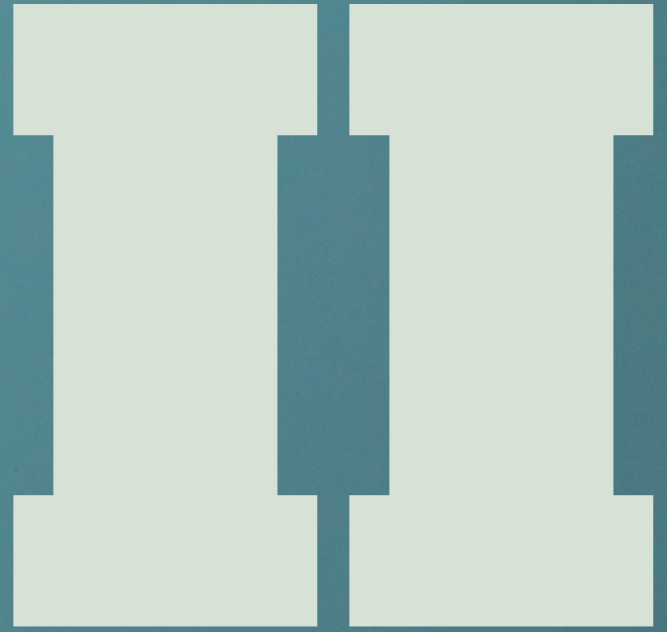
And I think it would be a disservice to the community if autistic people couldn't use these technologies on their own. How to make sure they're interpreting the information they get from wearables accurately is a huge responsibility. That is a challenge that will be hard and long to solve.

[This article was originally published in 2020.](#)

*Almost everywhere in the world that researchers look for autism, they are finding more of it than before—in girls as well as boys.*







# A Global Phenomenon



# Autism's Sex Ratio, Explained

BY NICHOLETTE ZELIADT

*The overrepresentation of boys among children on the spectrum is perhaps the most durable finding of autism research. But the measured ratio of males to females in the autistic population has shifted over time.*

Q

Autism is significantly more common in boys than in girls. This skewed sex ratio has been recognized since the first cases of autism were described in the 1940s. The exact reasons for the ratio remain unclear. It could be rooted in biological differences between the sexes. Or, some experts say, it may be an artifact of the way autism is defined and diagnosed.

Here's how researchers estimate and explain the sex ratio in autism.

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## *What is the sex ratio for autism?*

Researchers have consistently found more boys than girls with autism when estimating the condition's prevalence. This has been true regardless of whether the data came from parent-reported diagnoses, reviews of school and medical records, or diagnostic evaluations of children.

The most comprehensive analysis of autism's sex ratio, published in 2017, drew on data from 54 prevalence studies worldwide. That analysis estimated about 4.2 boys with autism for every girl.

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## *What factors might alter this sex ratio?*

One potentially important factor is diagnostic bias: Several studies suggest that girls receive autism diagnoses later in life than boys, indicating that the condition is harder to spot in girls.

In line with this idea, the 2017 study revealed that the sex ratio falls to 3.25 boys per girl when the analysis includes only the 20 studies in which researchers evaluated the participants for autism, rather than relying on previous diagnoses. This drop in the ratio provides

the most compelling evidence yet for a diagnostic bias, says the study's lead investigator William Mandy, senior lecturer in clinical psychology at University College London. "It implies that there's a group of females out there who, if you assess them, will meet criteria, but for whatever reason they're not getting assessed."

*Why are girls and women with autism being overlooked?*

Girls and women with autism may go undiagnosed because doctors, teachers, parents and others often think of the condition as primarily affecting boys.

Autism may also look different in girls than it does in boys. Girls may have fewer restricted interests and repetitive behaviors than boys do, and may have more socially acceptable types of interests. They are also more likely than boys to mask their autism features by copying their neurotypical peers. As a result, autism may be more difficult to detect in girls even when doctors are looking for it.

*Would the sex ratio disappear if these diagnostic biases could be overcome?*

Probably not. Researchers have found a 3-to-1 ratio even when they have followed children from infancy and repeatedly screened them for autism, minimizing the possibility for biases in diagnosis and referral. The children in these studies have a family history of autism, however, so they may be

fundamentally different from other children with the condition, says Daniel Messinger, professor of psychology at the University of Miami.

*Has the sex ratio changed over time?*

Yes. A large Danish study found an 8-to-1 sex ratio for autism in 1995, but that had dropped to 3-to-1 by 2010. The drop may reflect better detection of girls with autism, but is likely to level off. "I would put my money on 3-to-1," says Meng-Chuan Lai, assistant professor of psychiatry at the University of Toronto.

*What else could explain the sex ratio?*

Biology. For example, the brains of people with autism show patterns of gene expression that look more like those of typical males than typical females. Some of these genes are specific to microglia, immune cells in the brain that clear away debris and sculpt neuronal connections.

It is also possible that girls are somehow shielded from the condition. Girls with autism tend to have more mutations than boys with the condition. And boys with autism seem to inherit their mutations from unaffected mothers more often than from unaffected fathers. Together, these results suggest that girls need a bigger genetic hit than boys to have autism.

[This article was originally published in 2018.](#)

# FOR GIRLS, THE PATH TO AN AUTISM DIAGNOSIS IS FILLED WITH HURDLES

BY GEORGIA LOCKWOOD-ESTRIN

*For a variety of reasons, including sexism, many autistic girls are probably still being missed.*

An autism diagnosis can affect people in many different ways. For some, it can be negative and put up additional barriers to education and employment. For others, however, it can be positive and open the doors to the support that they and their family need. It can also bolster someone's sense of self and belonging within the autistic community.

Whether positive or negative—or, more likely, a mix of both—there is no denying that having a diagnosis makes the difference between accessing healthcare and support, or receiving nothing at all. But the journey to diagnosis is often lengthy, confusing and frustrating, which is problematic because early intervention is known to positively influence outcomes for autistic individuals and their families.

The barriers to diagnosis are especially challenging for women and girls. The research community is recognizing more and more that autistic women and girls are poorly served by the current clinical criteria and typical routes to a diagnosis.

What's happening that leads to a later diagnosis, and delayed intervention and support, for girls compared with boys? My colleagues and I sought to investigate why in a review published in October 2020 in the *Review Journal of Autism and Developmental Disorders*. A big part of the problem, we found, is the ongoing perception that autism is a 'male' condition.

## LAYERS OF BIAS:

Historically, researchers, clinicians and other experts have not viewed autism as a female condition. From the first published descriptions of autism by Leo Kanner and Hans

Asperger, most cases were described in boys and men.

Estimates of autism prevalence have found that boys are about four times as likely as girls to have a diagnosis, but the ways in which these estimates are calculated likely reflect biases in our perception, assessment and diagnosis of the condition. Prevalence estimates that reduce this bias put the sex ratio as low as 1.8 to 1.

Even before the diagnostic odyssey begins, boys are referred for an autism diagnosis 10 times as often as girls. And even with similar levels of trait severity, women and girls are less likely to be diagnosed than boys and men.

Women and girls with autism, even when they are referred, are diagnosed later than boys and men with the condition, studies show. This delay appears to exist despite there being no difference in how many visits they make to healthcare professionals, the age at which parents first express concern or the duration of their clinical assessments. They also experience greater stigma after they are diagnosed: For example, people are less likely to believe girls and women have autism than boys with the diagnosis.

My colleagues and I at Birkbeck College and King's College London in the United Kingdom systematically searched the literature for results that might shed light on the potential barriers to an autism diagnosis for girls and young women. We found 13 quantitative, 6 qualitative and 1 mixed-methods paper meeting our inclusion criteria.

## SHIFTING PERSPECTIVE:

Our analysis of these papers highlighted that in many cases, girls and women are diagnosed with autism only when certain traits, such as behavioral or language difficulties, are exaggerated, compared with boys and young men. This skew may be particularly problematic because girls and women, more often than boys and men, compensate for or mask aspects of their autism characteristics, according to many reports.

This masking is often referred to as 'camouflaging.' For example, autistic girls at school may intentionally or unconsciously hide their social communication difficulties in social situations, perhaps by mimicking the facial

expressions of others. Camouflaging is a key reason why girls and women may not come to clinical attention and fail to reach diagnostic thresholds during assessments.

We found one overarching barrier that affects all levels of identification and diagnosis in girls and women: Autism is widely viewed as a ‘male’ condition.

Not only did parents initially face disbelief and skepticism from others when they expressed concerns about their daughters and the possibility of an autism diagnosis, but they were often met with mixed messages from clinicians and health professionals about the girls’ autism characteristics. In one paper we reviewed, a parent commented to one set of researchers, “I remember her [pediatrician] saying that this is usually a boys’ thing and she is only a little different.”

In some cases, parents said they felt like they had to exaggerate their daughter’s traits in order to obtain a diagnosis. “I felt that I needed to make my daughter look more impaired than she actually was, in order to get diagnosis and needed services,” one parent told another set of researchers.

Current male-centric ideas about autism are prevalent in our society and are detrimental to autistic girls and women and their families trying to get a diagnosis and much-needed support. To improve access to services for girls and women in a meaningful way, the general public’s, as well as clinicians’ and researchers’, perceptions of autism must change. There is a vital and urgent need for widespread recognition that autism occurs in both sexes and all genders. We need more research on autism in girls and women—and more effective dissemination of that knowledge to those in front-line positions, such as doctors, teachers and parents.

*Georgia Lockwood-Estrin is a Sir Henry Wellcome postdoctoral research fellow at the Centre for Brain and Cognitive Development at Birkbeck College, University of London in the United Kingdom.*

This article was originally published in February 2021.

# Diagnosis Rates Are High Among U.K. Students as Well

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by LAURA DATTARO, JACLYN JEFFREY-WILENSKY

*As in the United States, the prevalence numbers vary by race and ethnicity, particularly among boys.*

About 1.8 percent of schoolchildren in England are autistic, according to one of the largest autism prevalence studies to date. The prevalence is highest among Black children—about 2.1 percent.

The findings, published in *JAMA Pediatrics*, represent a slight uptick from a 2009 estimate of 1.6 percent. A 2020 study put the country's prevalence at 2.3 percent.

The analysis draws on 2017 data from more than 7 million children aged 5 to 19 in England's National Pupil Database, which tracks school enrollment.

The team identified 119,821 students diagnosed with autism, or a prevalence of 1.76 percent, after adjusting for age and sex; 21,660 of them, or 18 percent, also have intellectual disability or a learning disability, such as dyslexia.

Students who have ever been eligible for free school meals—a marker of low socioeconomic status—are more likely to be autistic than those who have not. Socioeconomic disadvantages in comparison with white students accounted for more than 12 percent of the increased autism prevalence among Black and multiracial children, the researchers found.

Until recently, Black children in the United States were less likely to be diagnosed with autism than their white and Asian peers, although studies in both the U.S. and Europe have found higher rates of autism among children of immigrants, including some Black children.

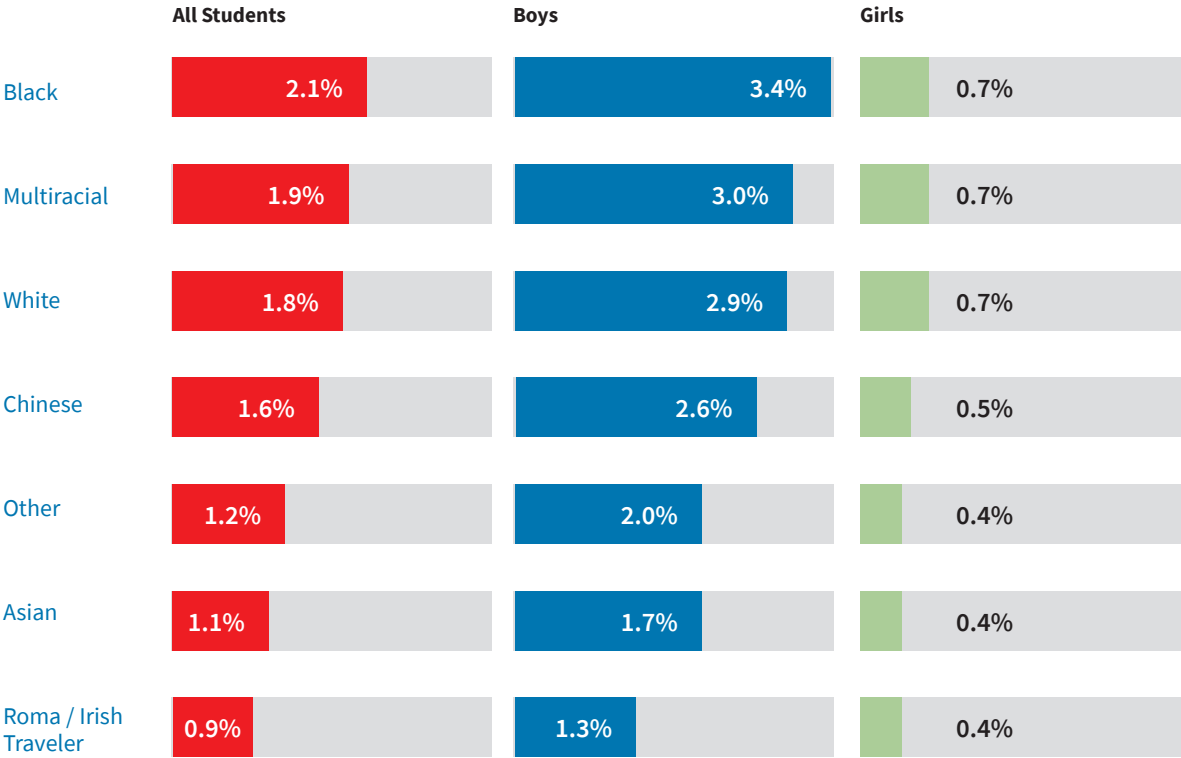
In the new study, however, children who speak a language other than English at home were less likely to have an autism diagnosis than those whose primary language is English.

The findings suggest a need to better understand how health policy, race, ethnicity and socioeconomic status intersect with autism and access to services, the researchers write.

[This article was originally published in March 2021.](#)

## PROPORTION OF ENGLISH SCHOOLCHILDREN WITH AUTISM

Autism prevalence is highest among Black children and lowest among Roma or Irish Traveler children. Across all groups, autism is more common among boys than girls.



The researchers calculated autism prevalence among 7 million English schoolchildren included in the National Pupil Database. This chart excludes students whose race or ethnicity was not given.

# SEARCHING A SOUTH KOREAN TOWN FOR AUTISM, RESEARCHERS FOUND FAR MORE THAN THEY EXPECTED

BY DEBORAH RUDACILLE

*This landmark study estimated that prevalence was more than double that reported at the time in the United States. But it also showed how hard it is to account for the effects of selection bias and stigma.*

The first comprehensive autism study in South Korea has found that the prevalence of the disorder is more than double the number in the United States.

Three-quarters of the children identified in the study had not previously been diagnosed with autism, and most were attending mainstream elementary schools, according to the report, published in *The American Journal of Psychiatry*<sup>1</sup>.

Researchers aimed to screen the 55,266 children born between 1993 and 1999 in Ilsan, a residential community near the South Korean capital, Seoul. They succeeded in screening less than half that number, possibly due to the extreme stigma attached to an autism diagnosis in the country.

Parents of more than 23,000 children between 7 and 12 years of age enrolled in mainstream schools and of 103 children in special-needs schools filled out a 27-item Autism Spectrum Screening questionnaire.

Of 1,742 children in mainstream schools who screened positive for autism risk, the parents of 785 initially consented to a full diagnostic evaluation. But only 234 of those children returned for the follow-up. This low number may be due to the fact that researchers could not contact some of the parents and others decided not to participate.

Parents of 84 children who were either in the district's disability registry or special schools also provided consent: Of that number, the researchers fully assessed 52.

For the autism diagnosis, the researchers relied on cognitive tests, interviews and the two gold-standard assessment tools—the Autism Diagnostic Observation Schedule and the Autism Diagnostic Interview-Revised.

Based on these criteria, they diagnosed autism spectrum disorders in 60 percent of 172 children with no history of psychiatric or psychological services and 77 percent of 62 children with a psychiatric history in mainstream schools. They also identified more than 90 percent of the 52 'high-probability' children already registered in special-education schools as having autism.

Extrapolating these numbers to the total school-age population, the researchers calculated a prevalence of 2.65 percent, compared with roughly 1 percent prevalence in the U.S.

"No matter how we calculated the numbers, we came up with this rate that surprised us," says Roy Richard Grinker, professor of anthropology at George Washington University in Washington, D.C. and one of the investigators on the study.

Grinker points out that a total population study of any disease or disorder is likely to turn up a higher rate than previous estimates based only on known cases. "You are leaving no stone unturned, and if you look hard enough, you will find cases," he says.

## PUZZLING STATISTICS:

There are few studies of autism prevalence outside of the U.S. and Western Europe, and those have typically found far lower rates than the official U.S. estimate of 1 in 110 children. For example, reports this year found 27.2 cases of autism per 10,000 children in Brazil<sup>2</sup> and 51 per 10,000 children in Western Australia<sup>3</sup>.

Researchers say that lack of awareness about autism and poor medical infrastructure partly explain these low prevalence estimates.

"Crude estimates of autism rates show that a lot of discovery needs to be done," says Peter Bearman, professor of social sciences at Columbia University. "The real incidence



is higher than those crude estimates would indicate.”

Bearman was not involved in the new study, but has extensively researched social factors driving the 637 percent increase in autism diagnoses in California between 1987 and 2003. His team concluded that the ‘autism epidemic’ in that state is largely an epidemic of discovery.

The high rate of autism in the South Korea study requires further investigation, Bearman says. “This is an extremely interesting study, but it is one setting,” he says.

Grinker acknowledges that the high rates in the study may reflect a sampling bias.

Parents concerned about their child’s behavior may have viewed the Ilsan study as an opportunity to gain information and access to services, Grinker says. Meanwhile, those who saw no reason to participate may have opted out, driving up the proportion of affected children.

In South Korea, an autism diagnosis stigmatizes not only the affected individual, but his or her whole family. For that reason, the researchers expected parents not to report problems on the screening questionnaire.

“I thought maybe we wouldn’t get that many kids because people would be too frightened of the diagnosis,” Grinker says.

To his surprise, parents not only chose to participate but also viewed the focus groups he assembled as a kind of support group. “A lot of them had never talked to another parent of an autistic kid,” he says.

His colleagues are already following up with a study of 6,000 children in a second community in Cheonan, a city south of Seoul.

That study, funded by the Simons Foundation, SFARI.org’s parent organization, aims to include phenotyping of both the Ilsan and Cheonan groups, characterizing their symptoms in detail. The researchers also plan to reanalyze whole-blood DNA samples from the Ilsan group and collect saliva samples from the Cheonan children.

The researchers found that autism combined with intellectual disability is much more prevalent in the high-probability group—59 percent compared with 16 percent in the general population—already enrolled in the disability registry or attending special schools. Mean intelligence quotient scores are about 20 points higher in the

general population than in this group.

The researchers identified five times as many boys as girls with autism in the high-probability group, but that ratio dropped to twice as many boys as girls in the general population.

Whether a similar study would uncover a significant number of children with undiagnosed autism in the U.S. remains unresolved.

A revised U.S prevalence might not rise to 2.65, “but I think we’d come up with significantly higher rates than 1 in 110,” Grinker says. “I can’t imagine that anyone would argue that there is a total absence of [undiagnosed] autistic kids in our school system.”

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This article was originally published in 2012.

# AS IN THE UNITED STATES, WEALTHIER ISRAELI FAMILIES ARE MORE LIKELY TO INCLUDE A CHILD WITH AN AUTISM DIAGNOSIS

BY JESSICA WRIGHT

*A 2012 study finds autism to be nearly five times as common as it was reported to be in 2001.*

A 2012 study found that 48 of every 10,000 children in Israel have autism. This rate, published in the *Journal of Autism and Developmental Disorders*, is higher than previous estimates for Israel, but lower than the reported U.S. prevalence<sup>1</sup>.

In March 2012, the U.S. Centers for Disease Control and Prevention reported that 1 in 88, or about 114 per 10,000, children in the U.S. have autism. The reported prevalence in most other countries is significantly lower: For example, it is 27 per 10,000 in Brazil and 16 per 10,000 in China.

Explanations for this disparity include awareness of autism, the stigma associated with an autism diagnosis and differences in healthcare.

How researchers estimate prevalence can also significantly alter the findings. For example, a 2011 study in South Korea that screened a representative sample of all children in a population found a prevalence of 264 per 10,000<sup>2</sup>. If the researchers had relied on existing medical records, however, the prevalence would have been 80 in 10,000.

Epidemiological studies of autism in Israel have reported relatively low rates. A 2001 study found an incidence of 10 for every 10,000 people<sup>3</sup> and a 2012 study reported a prev-

alence of 36 per 10,000 people<sup>4</sup>. These studies relied on medical and healthcare records from treatment facilities and national organizations, such as the Israeli Ministry of Social Affairs.

In the 2012 study, researchers used medical records from Maccabi Health Services, one of four health maintenance organizations that provide nationalized health services in Israel. They compared 2,034 children between 1 and 12 years of age who have an autism diagnosis with 421,490 others in the same age range.

Fewer children in low-income groups have a diagnosis of autism than do those from wealthier families, the study found. This trend is line with prevalence studies in the U.S., and may result from differences in awareness and cultural stigma, the researchers say.

Prevalence in Israel may be lower than in the U.S. because children in Israel undergo more thorough assessments for autism diagnosis, the researchers say. For example, each child in Israel undergoes two separate evaluations. Also, clinicians are required to describe how the child's symptoms match the criteria for autism outlined in the Diagnostic and Statistical Manual of Mental Disorders.

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This article was originally published in 2012.

# Indian Study Identifies Many Children on the Spectrum Who Are Not Attending School

BY ALLA KATSNELSON

*By enlarging their search area and looking outside schools, scientists find about four times greater autism prevalence than reported just a year earlier.*

About 1 in 100 children in India under age 10 has autism, and nearly 1 in 8 has at least one neurodevelopmental condition. The estimates are based on the first rigorous study of its kind in the country.

The estimate for neurodevelopmental conditions is about 10 times higher than the 1.3 percent reported in India's 2011 census.

“That [was] a gross underestimation,” says Narendra Arora, executive director of the INCLIN Trust International, who led the new study<sup>1</sup>. “This [new estimate] requires public health action.”

Arora and his colleagues fanned out to five regions of India that differ economically and culturally, and went door to door to recruit children for evaluation. They recruited 20 children from each of 25 or 50 villages and municipal wards in each region. Altogether, they assessed 2,057 children aged 2 through 5 years and 1,907 children aged 6 through 9.

“This is the first ever community-based assessment of prevalence of neurodevelopmental disorders in children in India, and probably in the whole of the developing world,” says Arora.

The most common conditions the team identified are hearing impairments and intellectual disability. Nearly one in five children who has one neurodevelopmental condition also has a second condition.

The breadth of the communities covered and the direct assessment of the children makes the work especially powerful, says Mayada Elsabbagh, an assistant professor of psychiatry at McGill University in Montreal, who was not involved in the work.

“There are very few prevalence estimates from most of the world’s geography when it comes to neurological disorders—especially autism,” Elsabagh says. “The methodology [in the new study] is quite impressive. This is often not done even in high-income countries.”

#### CONSERVATIVE ESTIMATE:

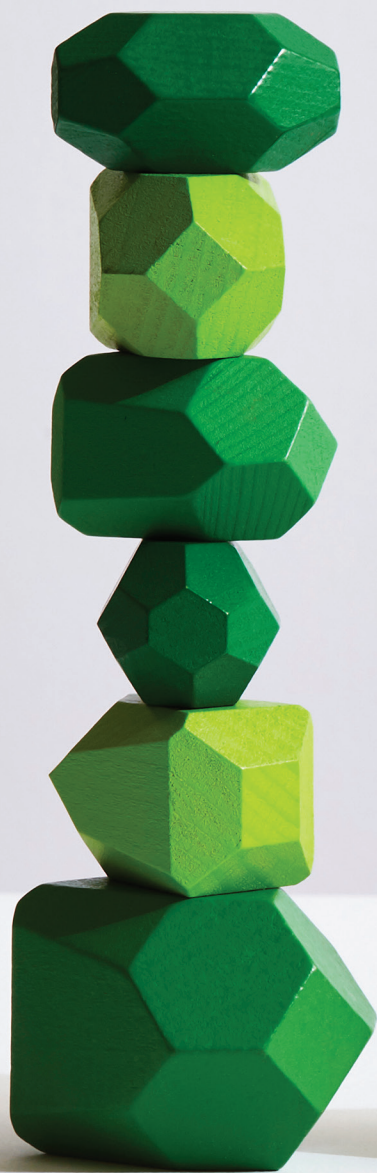
Arora and his colleagues had the children assessed

at nearby hospitals for vision and hearing problems, epilepsy, neuromotor conditions such as cerebral palsy, speech problems, autism and intellectual disability. Children aged 6 through 9 were also tested for attention deficit hyperactivity disorder and learning disorders.

The team diagnosed 44 children with autism, using a free test called the INDT-ASD they had developed for use in low-resource countries.

The overall prevalence of neurological conditions varies by region: For instance, it is strikingly low in a tribal area called Dhenkanal. Autism rates vary between 0.4 percent in North Goa, a largely urban coastal region, to 1.8 percent in Palwal, a rural area in north-central India. The work appeared in *PLOS Medicine*.

The overall prevalence estimate for autism is about four times that from a 2017 study of more than 11,000 schoolchildren in one city in India. The



higher number may result from the breadth of the sample: Arora's team recruited from the population at large, so the sample may include children who don't go to school, says Bhismadev Chakrabarti, professor of neuroscience at the University of Reading in the United Kingdom, who led the 2017 study.

That study used the Autism Diagnostic Observation Schedule (ADOS)—a diagnostic test that's standard in the United States and Europe—instead of the INDT, which makes it difficult to compare the results, Chakrabarti says.

Regardless, the new figures are likely to be conservative. About one in six families with children declined to participate, perhaps because of stigma associated with the conditions, Arora says. What's more, a smaller proportion of children in the study have developmental delays caused by poor nutrition than the national average, likely because the sample is not representative of the whole population.

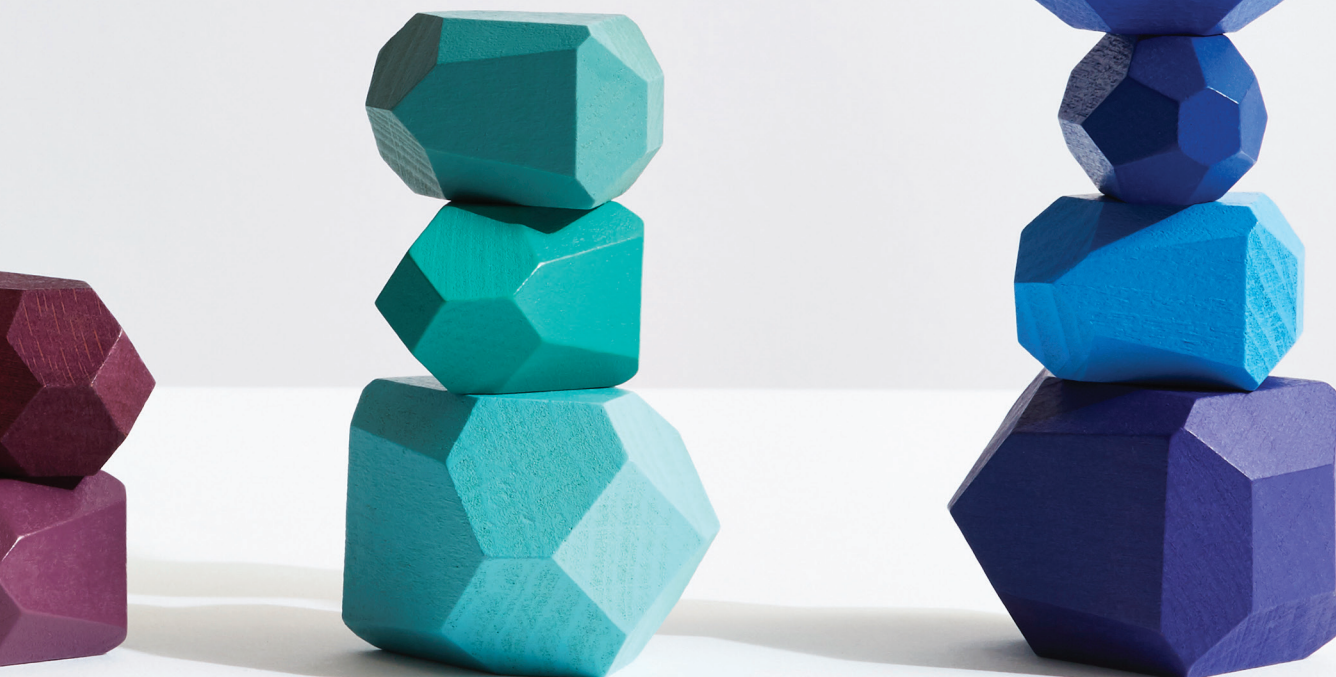
The study identified risk factors for developmental problems, such as home birth, serious childhood

illnesses and low birth weight, that the government can address. With a bigger study, Elsabbagh says, researchers might be able to determine which of these risk factors are most relevant to autism.

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This article was originally published in 2018.



# THE FIRST ESTIMATE OF AUTISM PREVALENCE IN QATAR IS “A WAKE-UP CALL”

BY HANNAH FURFARO

*Government officials are spurred to action by the report, which concludes that 1.4 percent of school-aged children have autism.*

The prevalence of autism among school-aged children in Qatar is 1.4 percent, higher than the worldwide average but lower than in the United States.

The findings come from the first reliable epidemiological study of autism prevalence in Qatar.

Researchers presented the results at the 2019 International Society for Autism Research annual meeting in Montreal.

Previous estimates suggested that about 5 in 10,000 children in Qatar are autistic, says Fouad Alshaban, senior scientist at Qatar Biomedical Research Institute in Doha, who presented the results. But these estimates were based on unreliable survey methods, he says, and are not considered accurate.

The new results have served as a wake-up call for government officials in Qatar, Alshaban says.

“This is very alarming to the authorities,” he says. “They are working very hard to provide the facilities for intervention for that number [of autistic people].”

Alshaban and his colleagues first translated into Arabic and validated a commonly used autism screen called the Social Communication Questionnaire (SCQ). They also trained doctors in Qatar to use gold-standard diagnostic tools, such as the Autism Diagnostic Observation Schedule.

The team sent the translated SCQ to the parents of more than 62,000 children aged 5 to 12 years. The parents of 9,074 children responded. Of the 773 children who screened positive for autism, 163 came in for a diagnostic evaluation. Clinicians diagnosed 14 of the children with

autism, including 5 for the first time.

Of the more than 8,000 children who screened negative for autism, 760 were evaluated for the condition, either in the clinic or via a parent phone interview. The researchers verified previous autism diagnoses in three children, but they did not identify any new cases.

Parents who are concerned about their children may be more likely than other parents to respond to the survey, which might have inflated the prevalence estimate. But this effect is likely to be “diluted by the very large sample size,” Alshaban says.

## SEX BIAS:

About 1.5 percent of 8-year-olds have autism—nearly identical to the prevalence in this age group in the U.S.

The researchers analyzed the medical records of an additional 839 autistic children who were seen in specialty clinics to estimate the male-female ratio for autism diagnoses and look at family characteristics, such as whether the parents are related to each other.

They found that autism is diagnosed in about four boys for every girl, in line with estimates in other countries. They did not find a relationship between the prevalence of autism and consanguinity—having parents who are first or second cousins. However, children whose parents are related are more likely to have severe autism traits.

The findings are likely to drive Qatar’s government to prioritize healthcare services for autistic people, Alshaban says. Healthcare in the country is largely paid for by the government.

This article was originally published in 2019.

# As Autism Prevalence Rises in Vietnam, so Does the Demand for Services

BY SARAH DEWEERDT

*The number of autistic people admitted to the pediatric hospital in Hanoi skyrocketed from 2000 to 2010.*

About 0.75 percent of young children in northern Vietnam have autism, according to a large study of children in the region<sup>1</sup>.

The study is part of a rare effort to systematically determine the prevalence of autism in the country and may represent the most accurate estimate yet.

Three other studies from 2012 to 2014, two of them unpublished, suggested a prevalence of 0.4 to 0.5 percent in northern Vietnam<sup>2</sup>. The new findings indicate that autism prevalence is increasing in the country, consistent with trends worldwide, says Thi Vui Le, vice head of demography and reproductive health at Hanoi University of Public Health.

The demand for autism services in the country is likewise growing: The number of autistic people admitted to the National Pediatrics Hospital in Hanoi increased threefold from 2000 to 2007 and fourfold from 2008 to 2010. Autism services in Vietnam are available mainly in major cities, Le says.

The new prevalence figure lines up with estimates from other low-resource countries. For example, autism occurs in about 1 percent of the population in India and China.

“It’s always nice to see data from underrepresented world regions, and the findings certainly contribute to filling important gaps in prevalence estimates,” says Mayada Elsabbagh, assistant professor of neurology and neurosurgery at McGill University in Montreal, who was not involved in the work.

### IMPRESSIVE SCALE:

Le and her team obtained lists of all children aged 18 to 30 months living in two provinces in northern Vietnam—Thai Binh and Hoa Binh—and the Vietnamese capital of Hanoi. They randomly selected about 2,000 names from nine lists—17,754 children in total.

They then sent trained local healthcare workers to the children's homes to administer a Vietnamese translation of the Modified Checklist for Autism in Toddlers (M-CHAT), a widely used screening questionnaire. The workers also collected information about the age, education level, occupation and annual income of each child's parents. About three-quarters of the children live in rural areas.

Of the 17,277 children whose parents completed the M-CHAT, 255 screened positive for autism. The researchers invited these children, and 340 others who screened negative, for a diagnostic assessment at local clinics. Pediatric neurologists at the clinics determined that 129 of the children who screened positive and one who screened negative have autism—a prevalence of 0.75 percent.

The doctors based their diagnoses on criteria in the fourth edition of the Diagnostic and Statistical Manual of Mental Disorders. They used these criteria rather than the newest criteria in the fifth edition so that the results could be compared with those from previous studies, Le says. The work appeared in the *International Journal of Mental Health Systems*.

The study's scale is impressive, says Bhismadev Chakrabarti, professor of neuroscience at the University of Reading in the United Kingdom, who was not involved in the work. "It's a very good and sys-

tematic effort in doing a population-based study in a setting where both awareness and research capacity is not very high," he says.

### PUZZLING PICTURE:

Autism is about four times as common in boys as in girls in Vietnam, consistent with patterns elsewhere. And it is nearly three times as prevalent in urban areas as in rural ones. This difference may be due to environmental factors, the researchers suggest, although the study was not designed to ferret out the reasons.

The prevalence of autism is close to five times higher among children of women who work as farmers (about 25 percent of mothers in the study) than among children of women employed by the government (16 percent of mothers).

This result is particularly puzzling, Chakrabarti says, as children of farming mothers tend to live in rural areas where prevalence is low, whereas children of government staff tend to live in urban centers.

"That is an unresolved issue and it's definitely worth probing further," he says.

Le's team is conducting a similar survey involving four provinces in the central and southern regions of the country. The researchers plan to screen 42,000 children in all.

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DOI:10.1186/s13033-019-0285-8
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This article was originally published in 2019.



# A Tale of Two Countries

BY PETER HESS

*In Catalonia, autism appears to be about as common as in the United States. Yet a study finds it to be far rarer in Iran.*

The first rigorous estimate of autism in Catalonia, Spain, has found a prevalence on par with that in the United States<sup>1</sup>. An independent study in Iran, meanwhile, has found a prevalence that lags far behind<sup>2</sup>.

The most recent reported prevalence in the U.S. is 1 in 40 and is based on 88,530 3- to 17-year-olds.

The reported prevalence in Catalonia, based on about 1.3 million children, was 1 in 81 in 2017 and had steadily risen over the previous nine years, according to the new study. In Iran, the reported prevalence is 1 in 1,000 and is based on 31,000 children.

The Iran team also set out to identify the prevalence of several conditions that often co-occur with autism, such as intellectual disability and attention deficit hyperactivity disorder (ADHD). The Catalonia study focused only on autism.

“A weakness of the [Catalonia] study is lack of information on co-occurring conditions such as intellectual disability, and information about sociodemographic variables,” says Maureen Durkin, professor of population health sciences and pediatrics at the University of Wisconsin-Madison, who was not involved in either study.

The team did chart prevalence over several years, however. They found that the proportion of diagnosed 2- to 17-year-olds rose from 0.07 percent in 2009 to 0.23 percent in 2017. In that final year, the sex ratio for autism diagnosis was roughly 4.5 boys for every girl. The study appeared in *Autism Research*.

The team also mapped autism prevalence geographically to establish a baseline for examining the relationship between environmental pollutants and autism. “In the process of getting the data and starting to set up the study, we thought it would be very relevant to do a first study,” says lead investigator Mònica Guxens, associate research professor at the Barcelona Institute for Global Health.

### EARLY DAYS:

The Iran team conducted informational and diagnostic interviews with 6- to 18-year-olds and their mothers. They found two boys were diagnosed with autism for every girl, but they saw no significant differences in prevalence for demographic variables such as parental education or urban versus rural residence—two factors that have skewed autism prevalence figures in U.S. studies.

They found that 86 percent of autistic children have at least one co-occurring condition: 70.3 percent have intellectual disability, 29.7 percent have epilepsy, 27 percent have problems with bladder control and 21.6 percent have ADHD. The study appeared in *Archives of Iranian Medicine*.

The Iranian team reported that mental health conditions such as schizoid personality disorder in the mother are associated with autism in the child. But Durkin says the lack of information about the father's mental health raises questions.

“This makes the paper read almost like a mother-blaming study from an earlier era,” she says.

The researchers also used a diagnostic tool that has “low agreement with autism diagnoses based on gold-standard tools,” Durkin says, which may explain the low prevalence they found. The tool, the Kiddie Schedule for Affective Disorders and Schizophrenia for School-Aged Children—Present and Lifetime, is reliable for diagnosing many psychiatric conditions, but not autism<sup>3</sup>.

Information on mental health was available only for mothers because the researchers did not survey fathers, says study-co-investigator Hadi Zarafshan, psychiatry and psychology researcher at Tehran University of Medical Sciences in Iran. And the team chose this tool because the study was part of an effort to investigate a range of psychiatric conditions—not just autism, he says.

### COMPLEMENTARY STRENGTHS:

The reported rates of intellectual disability and epilepsy among autistic people in Iran are unusually high. The researchers may have found only the most severe cases of autism, which might further explain their low prevalence estimate, researchers say.

“[It] probably isn't doing as great of a job at picking up less severe cases,” says Brian Lee, associate professor of epidemiology and biostatistics at Drexel University in Philadelphia, Pennsylvania, who was not involved in either study.

Lee notes that his team's previous work on a Swedish population showed an intellectual disability prevalence of 25.6 percent among autistic individuals<sup>4</sup>. “And because there is no good reason to suggest that the [autism] rate is different between geographic regions, I would think there is significant underdiagnosis,” he says.

Despite the caveats, the Iran study is valuable, he and Durkin say.

The study begins to fill gaps in information about autism prevalence in a country where, Durkin says, “the challenges of case ascertainment and absence of existing data systems” have created obstacles for researchers.

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This article was originally published in 2019.

# PREVALENCE MAP

LEARN MORE



Scan this QR code with your mobile device to use *Spectrum's* free interactive prevalence map and database, which includes links to all of the studies listed and plotted here.

## AUTISM AS IT IS MEASURED AROUND THE WORLD

*Spectrum's collection of prevalence studies published since the 1960s shows that, while measured rates of autism vary from region to region, they have been rising everywhere.*

By our reckoning, Victor Lotter kicked off the modern study of autism prevalence with his 1966 paper “Epidemiology of autistic conditions in young children,” which reported on the results of a study that screened all 8- to 10-year-olds in Middlesex County, U.K. for autistic behavior. It would be four years until another report of that kind was published.

Fast-forward to the present, and the question of autism prevalence has become a hot topic of research worldwide, with two dozen noteworthy prevalence studies published in 2018 and 2019 alone. The intervening half century saw the release of more than 150 distinct studies of this kind that, in the judgement of *Spectrum's* expert advisors, merit inclusion in our database of prevalence research. (For more details on that database and sample of the data, see “A Living Database of Prevalence Studies,” pages 92 – 93.)

The map on the following pages plots the locations of those studies, with darker dots marking those that are worth particular attention. The overall picture that emerges here and in the following table is both encouraging—in the quickening pace at which knowledge is accumulating—and sobering in the recognition that we still know so little about vast territories.

What appears here is just a snapshot of the interactive map and list available online from *Spectrum's* website at [prevalence.spectrumnews.org](http://prevalence.spectrumnews.org). There you can click on any dot to see the underlying data and follow a link directly to the research paper itself. Give it a try!

## NORTHERN IRELAND

The 2020/2021 school census found that autism diagnoses continue to become more common year after year in this part of the United Kingdom.

**6.7%**  
of boys

**2.2%**  
of girls

**4.5%**  
of all school-age children

## UNITED STATES

Multiple studies, varying in technique, have reported a bewildering range of prevalence estimates (see “How Common Is Autism in the United States? The Answer Depends on Which Agency You Ask,” page 15). But all the estimates have been rising over time.

**1.3%**  
Special Education  
Child Count  
(2017 data)

**1.8–1.9%**  
CDC ADDM  
Network  
(2016)

**2.2–2.7%**  
National Health  
Information  
Survey (2015–18)

**2.7–3.6%**  
National Survey  
of Child Health  
(2019)

## SCANDINAVIA

National health registries in Sweden, Denmark and Norway have enabled researchers to conduct very large prevalence studies.

**1.1–1.2%**  
Sweden  
(2012)

**2.6–3.0%**  
Denmark  
(2018, at age 16)

**0.43–0.59%**  
Norway  
(2012)

## LATIN AMERICA

Relatively few prevalence studies have been reported so far for this region.

**0.62–1.1%**  
Mexico (2016)

**0.13–0.2%**  
Venezuela (2008)

**0.07–0.24%**  
Argentina (2008)

## AFRICA AND THE MIDDLE EAST

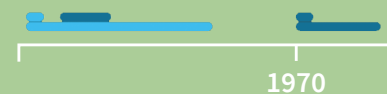
Recent studies in Nigeria, Lebanon and Qatar found autism to be common. But it is widely undermeasured throughout much of Africa and the Middle East.

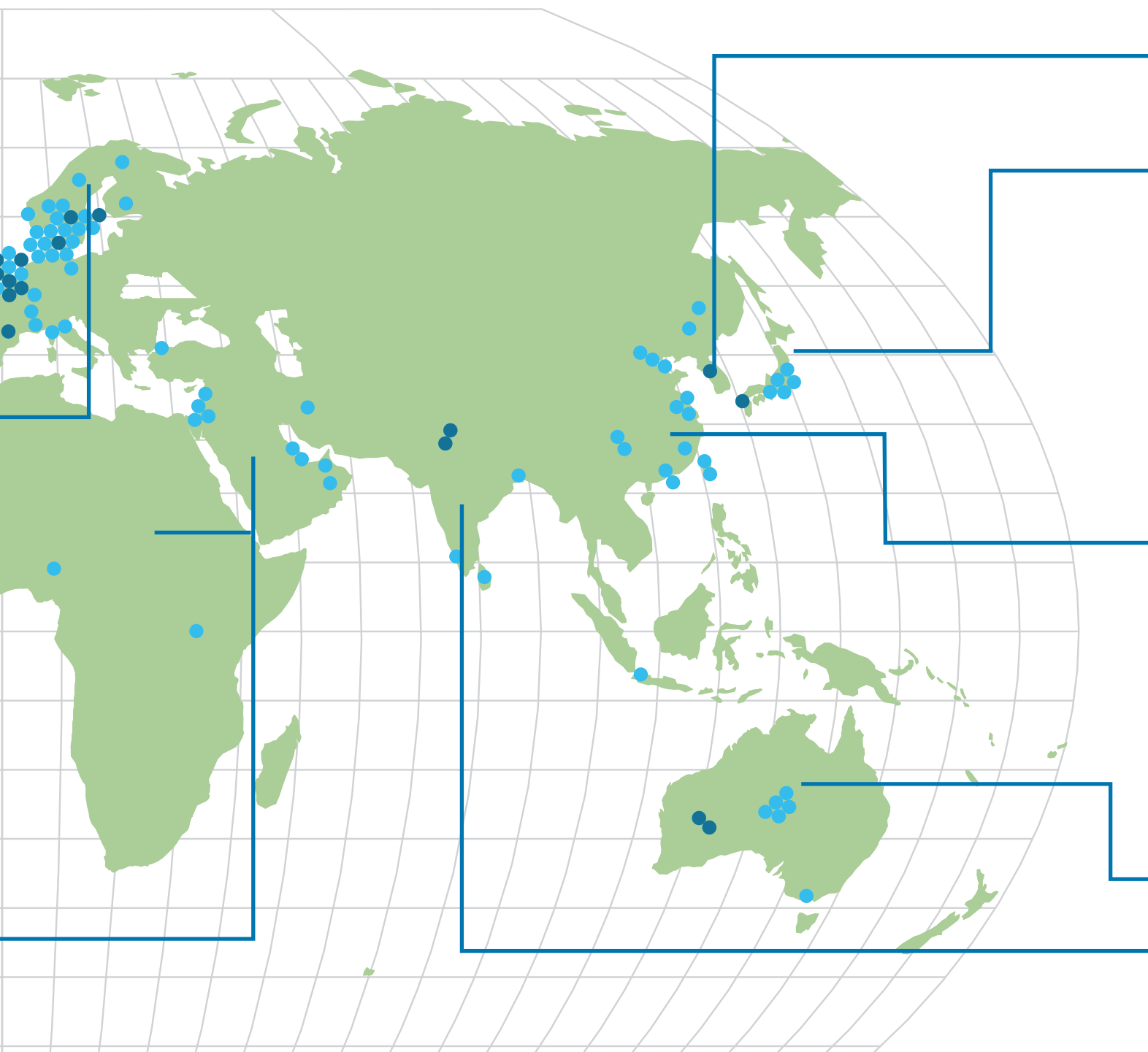
**1.7–4.1%**  
Nigeria  
(2016)

**0.77–2.3%**  
Lebanon  
(2016)

**0.89–1.5%**  
Qatar  
(2019)

## TIMELINE OF STUDIES (BY YEARS STUDIED)





### SOUTH KOREA

The first Asian country to conduct a community-wide survey of autism, South Korea's 2011 estimated prevalence of 1.9 to 3.4 percent sent reverberations around the world and helped spur case-finding techniques that gradually revealed autism to be far more common than previously appreciated (see "Searching a South Korean Town for Autism, Researchers Found Far More than They Expected" on page 78).

**1.9–3.4%**  
(2011)

### JAPAN

A long series of prevalence studies stretching back to 1982 has found autism to be on the rise in Japan, reaching 1.6 to 2.1 percent by 2008.

**1.6–2.1%**  
(2008)

### CHINA

Early estimates in 2000 found a low prevalence of just 0.3 percent in the city of Fujian. But studies since have improved the techniques they use to find autistic children, particularly those not in schools. Two studies published in 2019 reported prevalence numbers closer to those seen in Europe and North America.

**0.1–0.38%**   **0.2–0.89%**   **0.89–1.3%**  
Jiamusi   Shenzhen   Jilin  
(2019)

### AUSTRALIA

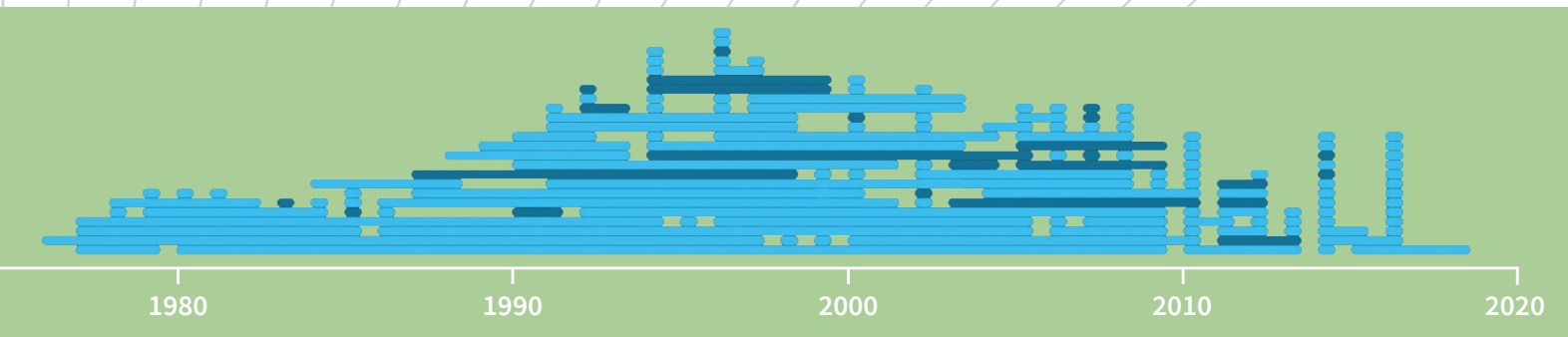
Over the past decade, measured autism prevalence in Australia has increased from well below 1 percent to an estimate of 1.6 to 2.9 percent reported in 2017.

**1.6–2.9%**  
(2017)

### INDIA

The largest study of autism in India to date found a prevalence of 1 to 1.4 percent in the regions of Palwal, Kangra, Dhenkanal, Hyderabad and North Goa. (See "Indian Study Identifies Many Children on the Spectrum Who Are Not Attending School" on page 81 for more details.)

**1.0–1.4%**  
(2018)



# A LIVING DATABASE OF PREVALENCE STUDIES

*Researchers are not yet certain whether autism is truly more common in some regions than others or whether the differences in estimates simply arise from geographic variations in how autism is diagnosed and measured.*

In 2018, as the pace of research into global autism prevalence seemed to snowball, the editors at *Spectrum* decided to compile results from prevalence studies around the world into a database, as a service to the autism research community. Consulting with *Spectrum's* expert advisors, the team selected a key set of parameters that are important for understanding these kinds of results (see list below) and then set about combing the literature to identify relevant papers and extract their key data.

It was a laborious effort, but it yielded not only a handy reference for researchers and policymakers but also a map that illustrates how our picture of autism prevalence around the world is filling in—and where significant gaps in knowledge remain.

The project continues to this day, with new studies added periodically to the database so that it reflects the latest work on this important question.

The table on the following pages includes just 118 of the 167 entries in the database as of this writing, and just a few of the most crucial bits of information about each study. To further explore the data or any of these studies, please point your mobile device's camera at the QR code on page 89 or aim your browser at prevalence.spectrumnews.org.

Each entry in the database records the following information about a prevalence study, where available:

- year published
- authors
- country
- area
- sample size
- age (years)
- individuals having autism
- diagnostic criteria
- percent having average IQ
- sex ratio (M:F)
- prevalence (per 10,000)
- 95 percent confidence interval
- category (AD, PDD or ASD)
- year(s) studied
- recommended by *Spectrum* advisors
- study type
- mean income of participants
- education level of participants
- citation
- article title
- article URL

YEAR	COUNTRY	AREA	PREVALENCE (PER 10,000)	95% CONFIDENCE INTERVAL	SAMPLE SIZE	AUTHORS
2008	Argentina	San Isidro	13	7.3–23.6	839	Lejarraga H. <i>et al.</i>
2009	Aruba	Aruba	53	41.0–66.6	13,109	van Balkom I.D. <i>et al.</i>
2004	Australia	Barwon	39	33.8–45.4	45,153	Icasiano F. <i>et al.</i>
2011	Australia	Western Australia	51	47–55.3	152,060	Parner E.T. <i>et al.</i>
2016	Australia		250	200–300	4,239	Randall M. <i>et al.</i>
2017	Australia	Western Australia	103	97.2–108	134,204	Fairthorne J. <i>et al.</i>
2017	Australia		240	160–290	4,164	May T. <i>et al.</i>
1988	Canada	Part of Nova Scotia	10	5.8–14.4	20,800	Bryson S.E. <i>et al.</i>
2006	Canada	Manitoba and Prince Edward Island	29	26.8–31.2	227,526	Ouellette-Kuntz H. <i>et al.</i>
2006	Canada	Montreal Island, Quebec	65	55.8–75.0	27,749	Fombonne E. <i>et al.</i>
2007	Canada	British Columbia	43		2,240,537	Ouellette-Kuntz H. <i>et al.</i>
2010	Canada	Montreal	79	67.8–90.4	23,635	Lazoff T. <i>et al.</i>
2014	Canada	Prince Edward Island, Newfoundland, Labrador and Southeastern Ontario	131	123.4–138.3	89,786	Ouellette-Kuntz H. <i>et al.</i>
2018	Canada	Québec	122	104–136	16,940	Diallo <i>et al.</i>
2000	China	Fujian	3	0.6–8.1	10,802	Luo W.W. <i>et al.</i>
2008	China	Hong Kong	16	14.9–17.3	4,247,206	Wong V.C. and S.L. Hui
2019	China	Jiamusi	19	10–38	16,358	Sun X. <i>et al.</i>
2019	China	Shenzhen	42	20–89	21,420	Sun X. <i>et al.</i>
2019	China	Jilin	108	89–130	7,258	Sun X. <i>et al.</i>
1970	Denmark	Aarhus County	4	2.4–6.2	46,500	Brask B.H.
2002	Denmark		7	5.0–10.0	63,859	Madsen K.M. <i>et al.</i>
2004	Denmark		12	11–13	682,397	Lauritsen M.B. <i>et al.</i>
2011	Denmark		69	65–72	404,816	Parner E.T. <i>et al.</i>
2012	Denmark		73	71.4–74.3	1,311,736	Parner E.T. <i>et al.</i>
2018	Denmark		37,280	13–88, 257–304	2,055,928	Schendel D.E. and E. Thorsteinsson
2000	Finland	North (Oulu et Lapland)	12	10.6–14.1	152,732	Kielinen M. <i>et al.</i>
2011	Finland	Northern Ostrobothnia County	84	61–115	5,484	Mattila M.L. <i>et al.</i>
1989	France	Rhône	5	3.4–5.6	135,180	Cialdella P. and N. Marnelle
1992	France	Aquitaine, Ile-de-France, Lorraine and Picardie	5	4.1–5.7	274,816	Fombonne E. and C. du Mazaubrun
1997	France	Haute-Garonne, Isère and Saône-et-Loire counties	5	4.6–6.1	325,347	Fombonne E. <i>et al.</i>
2015	France	Isère, Savoy, Upper-Savoy and Haute-Garonne counties	37	34.4–38.7	307,751	van Bakel M.M. <i>et al.</i>
1986	Germany	West Berlin	2	1.4–2.4	279,616	Steinhausen H.C. <i>et al.</i>
2001	Iceland		13	9.8–16.6	43,153	Magnússon P. and E. Saemundsen
2013	Iceland		120	106.6–135.3	22,229	Saemundsen E. <i>et al.</i>
2016	India	Kerala	23	17.3–31.3	18,480	Poovanthinal S.A. <i>et al.</i>
2017	India	Kolkata	23	7–46	11,849	Rudra A. <i>et al.</i>
2018	India	Palwal, Kangra, Dhenkanal, Hyderabad and North Goa	100-140	60–160, 60–320	3,964	Arora N.K. <i>et al.</i>
1992	Indonesia	Yogyakarta (southeast of Jakarta)	12	2.3–21.1	5,120	Wignjosumarto S. <i>et al.</i>
2011	Iran		6	5.84–6.70	1,320,334	Samadi S.A. <i>et al.</i>
1984	Ireland	East	4	2.7–5.9	65,000	McCarthy P. <i>et al.</i>
2001	Israel	Haifa	10	6.6–14.4	26,160	Davidovitch M. <i>et al.</i>
2013	Israel		48	45.9–50.1	423,524	Davidovitch M. <i>et al.</i>
2015	Israel		38	36.7–38.2	2,431,649	Raz R. <i>et al.</i>
2018	Italy	Pisa	80	62–97	10,138	Narzisi A. <i>et al.</i>
1982	Japan	Fukushima-Ken	2	1.9–2.7	609,848	Hoshino Y. <i>et al.</i>
1983	Japan		16	12–28	35,000	Ishii T. and O. Takahashi
1987	Japan	Kurume	16	11.3–19.8	32,834	Matsuishi T. <i>et al.</i>
1988	Japan	Southern Ibaraki	14	11.5–16.2	95,394	Tanoue Y. <i>et al.</i>
1989	Japan	Nagoya	13	6.7–19.4	12,263	Sugiyama T. and T. Abe
1996	Japan	Yokohama	21	11.4–30.8	8,537	Honda H. <i>et al.</i>
2005	Japan	Yokohama	38	31.0–45.0	32,791	Honda H. <i>et al.</i>
2008	Japan	Toyota	181	159.2–205.9	12,589	Kawamura Y. <i>et al.</i>
2016	Lebanon	Beirut, Mount-Lebanon	153	77–229	998	Chaaya M. <i>et al.</i>
2016	Mexico	Leon, Guanajuato	87	62–110	12,116	Fombonne E. <i>et al.</i>
2016	Nigeria		290	170–412	721	Chinawa J.M. <i>et al.</i>
1998	Norway	Akershus County	4	1.9–5.1	65,688	Sponheim E. and O. Skjeldal
2012	Norway	Oppland and Hedmark	51	43–59	31,015	Isaksen J. <i>et al.</i>
2011	Oman		1	1.2–1.7	528,335	Al-Farsi Y.M. <i>et al.</i>
2007	Portugal	Mainland and Azores	17	14.0–20.0	67,795	Oliveira G. <i>et al.</i>
2019	Qatar		114	89–146	133,781	Alshaban F. <i>et al.</i>
2011	South Korea	Goyang	264	191–337	55,226	Kim Y.S. <i>et al.</i>

YEAR	COUNTRY	AREA	PREVALENCE (PER 10,000)	95% CONFIDENCE INTERVAL	SAMPLE SIZE	AUTHORS
2009	Sri Lanka	semi-urban area	107	29.2–271.6	374	Perera H. <i>et al.</i>
1983	Sweden	Västerbotten County	6	3.9–7.4	69,000	Bohman M. <i>et al.</i>
1984	Sweden	Göteborg	2	1.3–3.0	128,584	Gillberg C.
1986	Sweden	Gothenburg and Bohuslan	5	3.1–6.2	78,413	Steffenberg S. and C. Gillberg
1997	Sweden	Mölnlycke	46	16.1–76.6	1,941	Arvidsson T. <i>et al.</i>
1999	Sweden	Karlstad	73	14.7–130.6	826	Kadesjö B. <i>et al.</i>
2006	Sweden	Göteborg	80	71.3–90.3	32,568	Gillberg C. <i>et al.</i>
2010	Sweden	Stockholm	22	19.4–25.0	113,391	Barnevik-Olsson M. <i>et al.</i>
2010	Sweden	Stockholm	62	52–72	24,084	Fernell E. and C. Gillberg
2012	Sweden	Göteborg	80	57–109	5,007	Nygren G. <i>et al.</i>
2012	Sweden	Stockholm County	115	112–118	444,154	Idring S. <i>et al.</i>
2011	Taiwan		29	26.6–31	229,457	Chien I.C. <i>et al.</i>
2014	Uganda	Kampala and Wakiso	120	58–182	1,169	Kakooza-Mwesige A. <i>et al.</i>
1966	United Kingdom	Middlesex	4	2.7–5.5	78,000	Lotter V.
1976	United Kingdom	Camberwell	5	2.1–7.5	25,000	Wing L. <i>et al.</i>
1997	United Kingdom	South Glamorgan, Wales	7	5.3–9.3	73,301	Webb E.V. <i>et al.</i>
1999	United Kingdom	North Thames	9	7.9–9.6	490,805	Taylor B. <i>et al.</i>
2000	United Kingdom	West Midlands	21	17.3–24.9	58,654	Powell J.E. <i>et al.</i>
2001	United Kingdom	England and Wales	26	16.2–36.0	10,438	Fombonne E. <i>et al.</i>
2002	United Kingdom	Cambridge	58	50.7–67.1	33,598	Scott F.J. <i>et al.</i>
2003	United Kingdom	Northeast London	31	27.9–32.9	186,206	Lingam R. <i>et al.</i>
2004	United Kingdom	Kent	24	9.6–49.1	2,536	Tebruegge M. <i>et al.</i>
2004	United Kingdom	Kent	83	51.3–126.3	2,536	Tebruegge M. <i>et al.</i>
2005	United Kingdom	Staffordshire	59	45.2–74.9	10,903	Chakrabarti S. and E. Fombonne
2006	United Kingdom	Scotland	44	39.5–48.9	134,661	Harrison M.J. <i>et al.</i>
2006	United Kingdom	South Thames, London	116	90.4–141.8	56,946	Baird <i>et al.</i>
2007	United Kingdom	Wales	61	53.9–69.4	39,220	Latif A.H. and W.R. Williams
2008	United Kingdom	Southwest (Avon)	62	48.8–74.9	14,062	Williams E. <i>et al.</i>
2009	United Kingdom	Cambridgeshire	94	75–116	8,824	Baron-Cohen S. <i>et al.</i>
2011	United Kingdom	England	98	30–165	7,333	Brugha T.S. <i>et al.</i>
2013	United Kingdom		24	22.2–26.0	256,278	Taylor B. <i>et al.</i>
1970	United States	Wisconsin	1	0.6–0.9	899,750	Treffert D.A.
1987	United States	North Dakota	3	2.4–4.1	180,986	Burd L. <i>et al.</i>
1989	United States	Utah	3	2.1–2.8	769,620	Ritvo E.R. <i>et al.</i>
2002	United States	Northern California	11	10.7–11.3	4,950,333	Croen L.A. <i>et al.</i>
2003	United States	Atlanta, Georgia	34	32–36	289,456	Yeargin-Allsopp M. <i>et al.</i>
2005	United States	Olmsted County, Minnesota	30	24.6–35.7	37,726	Barbaresi W.J. <i>et al.</i>
2007	United States	Northern California	45	41.2–48.4	132,844	Croen L.A. <i>et al.</i>
2007	United States	Alabama, Arizona, Arkansas, Colorado, Georgia, Maryland, Missouri, New Jersey, North Carolina, Pennsylvania, South Carolina, Utah, West Virginia and Wisconsin	66	63–68	407,578	Centers for Disease Control and Prevention
2009	United States	South Carolina	80	61–99	8,156	Nicholas J.S. <i>et al.</i>
2009	United States	Alabama, Arizona, Colorado, Florida, Georgia, Maryland, Missouri, North Carolina, Pennsylvania, South Carolina and Wisconsin	90	86–93	308,038	Centers for Disease Control and Prevention
2009	United States		110	94–128	77,911	Kogan M.D. <i>et al.</i>
2010	United States	Wisconsin	90	86.7–92.4	428,030	Maenner M.J. and M.S. Durkin
2011	United States	San Francisco Bay Area	47	42–51	82,153	Windham G.C. <i>et al.</i>
2012	United States	Alabama, Arizona, Arkansas, Colorado, Florida, Maryland, Missouri, New Jersey, North Carolina, Pennsylvania, South Carolina, Utah, West Virginia and Wisconsin	113	110–117	337,093	Centers for Disease Control and Prevention
2012	United States	Utah	130	118–142	33,757	Pinborough- Zimmerman J. <i>et al.</i>
2013	United States		200	191–209	95,677	Blumberg S.J. <i>et al.</i>
2014	United States	Alabama, Arizona, Arkansas, Colorado, Georgia, Maryland, Missouri, New Jersey, North Carolina, Pennsylvania, South Carolina, Utah, West Virginia and Wisconsin	147	142.9–150.7	363,749	Centers for Disease Control and Prevention
2015	United States		224	208–240	32,192	Zablotsky B. <i>et al.</i>
2016	United States	Arizona, Missouri, New Jersey, Utah and Wisconsin	134	125–144	58,467	Christensen D.L. <i>et al.</i>
2016	United States	Arkansas, Arizona, Colorado, Georgia, Maryland, Missouri, New Jersey, North Carolina, South Carolina, Utah and Wisconsin	146	142–150	346,978	Centers for Disease Control and Prevention
2016	United States	Minneapolis	207	183–234	12,329	Hewitt A. <i>et al.</i>
2018	United States	Arizona, Arkansas, Colorado, Georgia, Maryland, Minnesota, Missouri, New Jersey, North Carolina, Tennessee and Wisconsin	168	164–173	325,483	Centers for Disease Control and Prevention
2018	United States		250	223–281	43,021	Kogan M.D. <i>et al.</i>
2018	United States		250	221–279	43,032	Xu G. <i>et al.</i>
2019	United States	Arizona, Colorado, Missouri, New Jersey, North Carolina, Utah and Wisconsin	170	161–180	70,887	Centers for Disease Control and Prevention
2008	Venezuela	Maracaibo	17	13–20	254,905	Montiel-Nava C. and J.A. Peña

*The search continues for biological factors that might be contributing to increases in autism prevalence that researchers have measured.*





# III

## Changes in Biology and the Environment



# How Pregnancy May Shape a Child's Autism

BY MELINDA WENNER MOYER

*Autism is predominantly genetic in origin, but a growing list of preterm exposures for the mother and baby may sway the odds.*

Even after her first child, Shane, was diagnosed with autism last year at the age of 2, Melissa Patao knew she wanted a bigger family. She was aware that any other children she had would have high odds of being diagnosed with the condition—estimates suggest that about 20 percent of siblings of autistic children also receive a diagnosis—but she was more than willing to take the chance. “I just adore Shane so much; he’s my world,” she says. In August, Patao gave birth to her second son, Zayden.

If it turns out that Zayden is also on the spectrum, “so be it,” Patao says. But all through her pregnancy, she wondered ‘what if?’ She found herself poring over research studies in an attempt to understand his odds of having autism and what might influence them.

Patao, who is training to become a pediatric nurse practitioner, found no shortage of reading material: Last year alone, scientists published more than 100 papers on events during pregnancy that can influence a child’s odds of having autism. Genes determine about 50 to 95 percent of that risk. But that means that “there’s more to the story than just that genetic predisposition,” says Daniele Fallin, a genetic epidemiologist at Johns Hopkins University in Baltimore. Environmental contributions must also factor in.

The baby’s earliest environment—the womb—is critical: Because the fetal brain produces about 250,000 neurons every minute during pregnancy, experiences that interfere with that process can affect the developing brain in lasting ways. Studies have linked autism to a number of factors in pregnancy, among them the

mother's diet, the medicines she takes and her mental, immune and metabolic conditions, including preeclampsia (a form of high blood pressure) and gestational diabetes. Other preliminary work has implicated the quality of the air she breathes and the pesticides she is exposed to. And some research suggests that birth complications and birth timing may also play a role.

The relationship between many of these factors and autism is still speculative. "That question of causality, it's a burden that is very difficult to fulfill," says Brian Lee, an epidemiologist at Drexel University in Philadelphia. This is generally true of research into environmental exposures, and particularly so for studies in pregnant women: Researchers cannot ethically expose pregnant women to possible risks; observational studies can only identify correlations, not causes; and the results of animal studies do not always extrapolate to people.

But researchers are starting to uncover biological threads that tie some of these prenatal exposures together. Many affect common biochemical pathways previously implicated in autism, such as those involving inflammation and aberrant immunity in both mother and baby. Each may only "contribute a little bit of risk here and there," Lee says, but it is crucial.

#### INSIDE THE WOMB:

Autism has been tied to events throughout pregnancy, including the first few days after conception. Even before a tiny human blastocyst attaches itself to the nutrient-rich lining of its mother's uterus, factors that will shape its nervous system are already in play. In the days immediately following conception, genes that govern brain wiring are turned on and off in a process that requires folate, or vitamin

B9. Folate may be important for the building of fundamental brain structures later on, too.

If a mother's diet is deficient in folate, these processes can go awry, increasing the risk for neural defects, such as spina bifida and possibly autism. In a 2013 study, Norwegian researchers followed more than 85,000 women from 18 weeks into their pregnancies until an average of about six years after delivery, collecting information that included whether and when the women took supplements of folic acid, the synthetic form of folate, as well as the health of their children. Those who took supplements, especially between four weeks before and eight weeks after conception, were about 40 percent less likely to have children diagnosed with autism than those who did not take the supplements. Other studies have linked vitamin D deficiency in pregnant women with autism in their children, but the implications are unclear.

How strongly a blastocyst attaches to the mother's uterine wall after fertilization can affect its access to folic acid and other nutrients. A strong attachment ensures that the embryo connects with the mother's blood vessels and remodels them to supply it with nutrients and oxygen throughout pregnancy, says Cheryl Walker, an obstetrician-gynecologist at the University of California, Davis. By contrast, a shallow implantation can lead to fetal growth restriction and low birth weight, both of which are linked to autism.

A shallow attachment can also lead to preeclampsia in the mother. Children with autism are twice as likely as typical children to have been exposed to preeclampsia, according to a 2015 study. In a woman with preeclampsia, blood vessels in the placenta "don't dilate as well, and they don't end up giving as many resources to that baby," says

Walker, who was involved in the study. As a result, the fetal brain may be starved of nutrients it needs to grow properly.

The fetus' immune system can also interfere with its brain development. Certain molecules, called cytokines, that control the migration of cells in the immune system are also crucial for neurons and immune cells to get to their correct locations in the nervous system. "The two systems talk to each other in ways that we didn't realize they did," says Judy Van de Water, a neuroimmunologist at the University of California, Davis.

Infections during pregnancy may scramble this signaling. A successful pregnancy involves an intricate immune dance: A woman's immunity has to tamp down so that it does not attack the fetus as a foreign invader but also remain vigilant enough to ward off harmful infections. Even when that goes to plan, though, serious infections can ramp up her immune response, to the detriment of her child. For example, a 1977 study found a surprisingly high prevalence of autism—1 in 13—among children born to mothers who were infected with rubella during pregnancy. And a 2015 study that followed more than 2.3 million children born in Sweden from 1984 to 2007 reported that women who are hospitalized for infections during pregnancy have about a 30 percent increase in the odds of having a child with autism compared with other pregnant women.

That risk may be mediated at least in part by inflammation and disrupted immune signaling in the mother. A 2013 study of 1.2 million Finnish births found that women with the highest levels of C-reactive protein, a common inflammation marker, in their blood are 80 percent more likely to have children diagnosed with autism than women with the lowest levels. Last year, Van de Water and her colleagues reported that women who went on to have autistic children with intellectual disability had elevated blood levels of certain cytokines halfway through gestation.

Some cytokines seem to be particularly important in mediating autism risk. In mice, immune activation contributes to autism only when a subset of immune cells, called T-helper 17 cells, release a cytokine called interleukin 17. In mice without



these cells, inflammation during pregnancy does not seem to lead to autism. T-helper 17 cells are produced in response to specific gut bacteria, raising the possibility that pregnant women with these bacteria are especially susceptible to the kind of inflammation that contributes to autism. Eliminating those specific bacteria from pregnant women's guts might lower the odds of autism in their children—a possibility researchers are investigating.

Obesity, diabetes before and during pregnancy, stress and autoimmune conditions in the mother have been associated with autism in her child, too: All either induce inflammation or impair immune signaling in other ways. These pieces of evidence, taken together, are called the 'maternal immune activation hypothesis.' A meta-analysis of 32 papers published earlier this year found that women who are obese or overweight before pregnancy are 36 percent more likely than women at a healthy weight to have children later diagnosed with autism.

Van de Water's work has shown that some autoimmune reactions can even directly damage the fetal brain. (During pregnancy, a woman's antibodies can cross the placenta and even cross the fetal blood-brain barrier.) In 2013, Van de Water's team reported that 23 percent of mothers of autistic children carry antibodies to fetal brain proteins,

compared with 1 percent of mothers of typical children. No one knows why these women might have these antibodies—it's "the \$50 million question," Van de Water says—but researchers posit they may be yet another byproduct of a maternal immune system gone haywire. Factors outside the mother's body can also wield powerful effects.

#### OUTSIDE THE WOMB:

Manish Arora's desk at the Icahn School of Medicine at Mount Sinai in New York City is a chaotic jumble of half-empty coffee mugs, philosophy books and baby teeth. The tiny teeth were donated for a study unrelated to autism, but they may uncover secrets about the condition nonetheless, he says.

Arora is many things: a dentist, a scientist and a father to 6-year-old triplets. He is soft-spoken and often speaks in metaphors. In his professional life, he strives to understand how chemical exposures early in life affect brain development, a passion shaped by his childhood growing up on the border of Zambia and what is now Zimbabwe. He remembers trucks spraying pesticides such as DDT on the ground—and sometimes also on children playing outside—to control malaria, a practice that he continued to think about as he got older because of its potential harm.

As Arora knows from his dentistry work, baby teeth provide a record of a body's chemical exposures. Teeth, he explains, are like trees: As they grow, they create rings—about one-tenth the diameter of a human hair—that record the chemicals and metals they encounter. These growth rings begin to form at the end of the first trimester of gestation and continue throughout life. "Today, you and me are forming a growth ring and it's capturing everything that we're exposed to," he says. By studying the



growth rings of discarded baby teeth, he and his colleagues can analyze what fetuses were exposed to in utero. The stress of birth creates a dark mark that can be used as a reference point.

In May, Arora and his colleagues reported an analysis of baby teeth collected from 193 children, including 32 sets of twins in which one twin is autistic and the other is not. The team analyzed the children's tooth growth rings using a highly

and 1960s and later found to cause serious birth defects. Valproate, a drug used to treat epilepsy, bipolar disorder and migraines, is also linked to autism when taken during pregnancy. But for other common drugs, such as antidepressants, an association with autism is harder to discern.

Part of the problem is that women take antidepressants for underlying mental-health conditions—so if an association is found, it is often unclear

*“We’re starting to put things together that we never, ever thought to look at in combination.” —Van de Water*

sensitive form of mass spectrometry. The levels of metals such as zinc and copper typically cycle together in a pattern—both metals help to regulate neuronal firing—but in autistic children, the cycles are shorter, less regular and less complex than in controls. Arora's team created an algorithm based on these group differences that can predict a child's autism with more than 90 percent accuracy.

Arora's work is part of a growing field that is attempting to decipher what kinds of environmental exposures increase the odds of autism and how they interact with human biology and genetics. These are tough questions to answer. Researchers cannot easily collect blood or saliva samples from fetuses to see what's circulating through them. Instead, they try to discern fetal exposures by using the mother's environment as a proxy. If a pregnant woman takes a particular medication, for instance, researchers can extrapolate that the fetus, too, was exposed.

So far, though, results have been mixed. Studies suggest that autism is associated with thalidomide, a drug prescribed for morning sickness in the 1950s

whether the root cause is her medication or her genetics. “It's very difficult to disentangle,” says Hilary Brown, an epidemiologist at the University of Toronto Scarborough in Canada. Last year, through a clever study design, she and her colleagues inched a bit closer to the truth. They studied sibling pairs in which one sibling had been exposed to antidepressants in utero and the other had not, allowing them to control for the severity of the mother's depression, among other factors. They reported that the siblings exposed to antidepressants were no more likely to have autism than their unexposed siblings. The results suggest that the medications themselves do not increase autism risk.

Some research has also linked the use of acetaminophen (commonly marketed as Tylenol) during pregnancy to autism. But again, it is unclear whether it is acetaminophen that is the problem, or the underlying reason for its use—pain or an infection, leading back to the maternal immune activation hypothesis.

Air pollution might also be linked to autism risk, but the details are hazy. At least 14 studies have sug-

gested an association with autism, and air pollution is known to trigger inflammation, but analyses of individual airborne chemicals have been inconsistent. Researchers are also confused by the fact that cigarette smoking, which contains many of the same chemicals as air pollution, is not associated with the condition.

Certain pesticides, such as chlorpyrifos, can disrupt sex-hormone pathways implicated in animal models of autism. But again, studies linking pesticides to autism have been mixed, and questions about causation are unresolved. More answers may emerge, however, as researchers uncover new ways to study interactions between fetuses and the outside world. In addition to Arora's work on baby teeth, researchers are investigating what kinds of chemical stories meconium, a newborn's first feces, can tell.

#### BIRTH AND BEYOND:

Princeton University neuroscientist Sam Wang has long been interested in autism's potential environmental causes, but he says he finds the research intimidating. "It's like the sands of the seas," he says. "It's this enormous literature, and people who work in it have all these different perspectives."

Several years ago, in an attempt to bring clarity to the issue, Wang perused about 100 studies and then ranked dozens of associations between autism and both genetic and environmental factors by their relative risk ratios. He described his findings in a 2014 op-ed in *The New York Times*.

What came out on top in Wang's analysis of environmental factors was birth—in particular, rare birth injuries to the cerebellum, a brain region that coordinates muscle movements, among other functions. "If it's a difficult birth, or there's a bleed on the cerebellum, then that increases the risk of

autism dramatically," by a whopping 3,800 percent, he says. "It's bigger than any other risk factor, other than sharing your entire genome with a person with autism." Wang's research supports the link, too: He has shown that mice with early damage to the cerebellum later have serious cognitive and behavioral problems that mimic autism traits.

The timing of birth also made Wang's list: Babies born at least nine weeks premature seem to have higher odds of autism, he found.

When Noelle Mathias found out she was pregnant with her eldest daughter, Elena, in 2008, she took good care of herself. Mathias exercised, ate well and didn't drink alcohol or smoke. "As far as I knew, it was a normal pregnancy," she recalls. But her water broke early at 36 weeks and Elena was born less than 24 hours later. When Elena was 2, Mathias and her husband noticed she wasn't responding to her name. They had Elena evaluated and, soon after, the girl was diagnosed with autism.

It's impossible to know whether Elena's preterm birth played a causal role in her diagnosis. Is being born early itself the issue, or might an underlying genetic susceptibility or environmental insult increase the odds of both preterm birth and autism?

Mathias' second pregnancy was full term, and her daughter Elisa, now 8, is developmentally typical. But in Mathias' third pregnancy, her water broke at only 25 weeks and she spent 53 days in the hospital on bed rest, hoping to delay birth as long as possible. Her son Emmanuel held out until 33 weeks and then spent time in the neonatal intensive care unit. He's 2 now and seems to be developing typically.

Mathias has no idea why her first child has had a different outcome from the others. Parsing the risk for any one child is complicated by the fact that autism "isn't just a 'you have it or you don't'

condition—it's this wide phenotypic spectrum," says Kristen Lyall, an epidemiologist at Drexel University's A.J. Drexel Autism Institute. Perhaps some environmental factors preferentially influence social skills, whereas others primarily shape cognitive development, for instance.

It may also be that certain combinations of factors—several environmental exposures in a row, perhaps, or a particular exposure along with a genetic susceptibility—are necessary to tilt a child's brain development toward autism. A 2016 study, for example, found that in mice, maternal infection can modulate the effects of genes linked to autism, including CNTNAP2. "We're starting to put things together that we never, ever thought to look at in combination," Van de Water says. "You've got people working together that never would've necessarily crossed paths." As part of those efforts, researchers are looking for fetal and infant biomarkers of autism, such as irregular cytokine profiles, anti-fetal antibodies and markers of oxidative stress, which might open the door to earlier and more effective interventions.

Because Zayden has an older brother with autism, Melissa Patao was able to enroll him in a 'baby sibling' study at the Yale Child Study Center. Researchers there followed Patao's pregnancy with Zayden and plan to continue to track his development into toddlerhood. For now, Zayden is doing everything a 3-month-old usually does: He is smiling and interacting with his family, and he recently started laughing. His brother Shane is also doing well—he is engaging in pretend play and his language skills, which are only slightly delayed, are continually improving.

Patao welcomes the fact that Zayden will be monitored so closely. She and her husband will know if he shows autism traits early, and he will have access to recommended interventions at the youngest possible age, when they are known to have the largest impact. "Being part of this study was something so meaningful for me," Patao says. "It totally took away the overwhelming anxiety of wondering, 'what if?'"

[This article was originally published in 2018.](#)



# HOW IMPORTANT ARE THE MUTATIONS THAT OLDER FATHERS PASS ON TO THEIR AUTISTIC CHILDREN?

BY POLINA POROTSKAYA

*One study finds that mutations in sperm may accrue too slowly to greatly increase autism risk.*

A 2019 analysis challenges the idea that mutations in the sperm of older fathers account for higher rates of autism in their children<sup>1</sup>.

Spontaneous, or ‘de novo,’ mutations are known to accumulate in sperm over time—leading some researchers to suggest that these mutations explain why men aged 50 or older are twice as likely as men under 30 to father an autistic child.

But a statistical model developed by a team at the Broad Institute in Cambridge, Massachusetts, suggests that de novo mutations account for less than 10 percent of the increase in risk.

To quantify the risk associated with paternal de novo mutations, the team first estimated the rate at which these mutations accumulate in sperm in the general population. They used the Simons Simplex Collection (SSC), a large repository of sequences from autistic children and their unaffected family members. The researchers looked specifically at 1,827 control ‘trios’—two parents and one neurotypical sibling of the autistic child. (The SSC is funded by the Simons Foundation, *Spectrum’s* parent organization.)

They determined that de novo mutations accumulate in sperm at a rate of 3.1 percent each year: A typical 20-year-old man passes on to his children only 0.44 de novo mutations, whereas a typical 40-year-old passes on 0.81 mutations.

The team turned to sequencing data from multiple

studies—including some based on the SSC—to estimate the impact of de novo mutations on five conditions, including autism and schizophrenia. They calculated that each de novo mutation above the baseline increases the risk for autism by about 9 percent.

Because the mutations accumulate slowly, however, a child would need to be born to a 45-year-old father to be 9 percent more likely to have autism than if the father were 25 years old, according to the model.

“It takes several decades of aging before the expected number of de novo mutations is even one higher than the baseline rate,” says lead investigator Jacob Taylor, a psychiatrist at Harvard University. “This work quantifies the idea that the mutations don’t accumulate fast enough to cause a huge increase in [autism] risk.”

## MAKING ASSUMPTIONS:

The team also compared their estimates with epidemiological data from the Danish National Health registry for people born between 1955 and 2012. They found that the number of people diagnosed with autism in that time period exceeds their model’s predictions by nearly an order of magnitude. The findings were published in *Nature Communications*.

The discrepancy suggests that something other than de novo mutations in sperm accounts for the increased incidence, they say.

One explanation is that men who have children at a later age may also be more likely to carry other genetic factors related to autism. “They may also be slightly more likely to have a child with autism regardless of when they actually do have kids,” Taylor says.

Those children may have older mothers; women older than 40 are more likely to have autistic children than women younger than 30, according to some studies.

The researchers did not control for mothers’ age because mothers and fathers are often similar in age, and because de novo mutations occur three to four times more often in sperm than in egg cells.

But older women may be more likely to have children with autism for other reasons, including a higher risk of preterm birth, gestational diabetes and complications

in pregnancy and delivery, says Maureen Durkin, professor of population health sciences and pediatrics at the University of Wisconsin-Madison, who was not involved in the study. “I think it’s a stronger confounding variable than they think.”

Also, to simplify their calculations, the Broad team assumed that all de novo mutations carry an average amount of risk and accumulate at the same rate.

“We know that of course not every mutation is equivalent,” Taylor says, but he adds that there is no reason to believe autism-related mutations accumulate any faster than others.

The Danish sample the researchers chose might also overestimate the prevalence of autism, says Kenny Ye, associate professor of biostatistics and system biology at the Albert Einstein College of Medicine in New York City, who was not involved in the study. A previous analysis found that autism’s prevalence in Denmark is 3.1 percent, compared with 1.2 in Finland and 1.7 in the United States<sup>2</sup>.

However, Ye says the study does suggest one possibility: In men who carry some mutations related to autism, but not enough to have the condition themselves, de novo mutations might tip the balance toward diagnosis in their children.

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# IMPROVED CARE FOR PREEMIES MAY CONTRIBUTE TO HIGHER AUTISM PREVALENCE

BY CHARLES Q. CHOI

*Recent research strengthens the link between premature birth and the risk of autism.*

Premature birth is tied to an increased chance of having autism, according to the largest study yet to examine the connection. And premature birth itself—rather than unrecognized genetic or environmental factors—seems to underlie the association.

The findings suggest that infants born prematurely need early evaluation and long-term follow-up to support the timely detection and treatment of autism, experts say.

“We know that early intervention can make a huge difference in later outcome, and more effective interventions are increasingly available,” says April Benasich, professor of developmental cognitive neuroscience at Rutgers University in Newark, New Jersey, who did not participate in this study.

Previous research suggests that babies born preterm—before the 37th week of pregnancy—have a roughly 30 percent higher chance of having autism than do those born full-term. Nearly 11 percent of births worldwide are premature, and more than 95 percent of these babies survive with modern neonatal care.

“Our prior work has shown that most children who were born preterm survive into adulthood without neurodevelopmental disorders or other chronic health problems,” says lead investigator Casey Crump, professor and vice chair of research in the family medicine and community health department at the Icahn School of Medicine at Mount Sinai in New York City.

But researchers have long debated whether preterm birth contributes to autism or whether both conditions might share genetic or environmental influences. It was also

unclear if the link shows a sex bias, or if it extends to early-term birth—during weeks 37 and 38 of pregnancy—which is roughly three times more common than preterm birth.

In the new study, researchers scoured national health-care and birth registries to analyze data for more than 4 million people born in Sweden between 1973 and 2013.

“I was bowled over by the cohort size,” Benasich says.

Both preterm and early-term birth were significantly linked to an increased likelihood of autism in both boys and girls. The earlier a baby was born, the higher her chances of having autism, the team found: About 6 percent of those born during weeks 22 to 27 of gestation have autism, compared with 2.6 percent of those born during weeks 28 to 33, 1.9 percent of those born during weeks 34 to 36, and 1.6 percent of those born during weeks 37 to 38. By contrast, 1.4 percent of babies born full-term—39 to 41 weeks—have autism.

The scientists detailed their findings in *Pediatrics*.

## FOLLOWING UP:

Comparisons with siblings further revealed that the link between prematurity and autism is not primarily explained by shared genetic or environmental factors within families. Instead, prematurity itself may slightly increase an infant’s chances of having autism.

“Although the relative risks of autism were significantly higher in persons born preterm than those born full-term, the absolute risk was still low—for example, only 2.1 percent of those born preterm were diagnosed with autism,” Crump adds.

Prematurity could up the chances of autism via inflammation of the brain and nervous system, Crump and his colleagues suggest. Premature infants often show altered connectivity between different parts of the brain, which may also underlie the neurodevelopmental problems that are common in this group, Benasich says. Understanding how such mechanisms contribute to autism in children born preterm or early-term could shed light on the causes of autism in general, she says.

“A better understanding of the mechanisms may potentially reveal new targets for intervention at critical windows of neurodevelopment,” Crump says.

Future research should collect individualized prenatal, perinatal and postnatal data to analyze what infants experience in neonatal intensive care, which could help identify key influences on autism and improve the quality of medical care, says Li-Wen Chen, clinical assistant professor of pediatrics at the National Cheng Kung University Hospital in Tainan, Taiwan, who did not take part in this work.

Though new study is limited to data from one country, Crump says, “we expect that the findings are likely to be generalizable to other settings, but they should be replicated in other populations when feasible.”

This article was originally published in August 2021.

# Are Epidurals Linked to Autism?

BY LAURA DATTARO

*Two large studies found no significant association between autism and this common form of anesthesia.*

The epidural anesthesia commonly given to pregnant people during labor is not linked to autism in children, according to two studies published in the *Journal of the American Medical Association*.

The results contradict a study published in October 2020 that seemingly connected epidurals among women in California to a slightly increased chance of autism in their children. That study drew widespread criticism and concern from researchers and professional medical societies for its failure to account for confounding factors, such as a family history of psychiatric conditions. In April 2021, a follow-up study in Manitoba, Canada, that controlled for some additional factors found no such association.

“There really is no solid evidence, from any of the studies actually, that epidural labor analgesia causes autism,” says Cynthia Wong, professor of anesthesia at the University of Iowa in Iowa City, who co-wrote a commentary accompanying the new studies. “I don’t think either clinicians or parents at this point in time need to take that consideration into account.”

The two new studies probe the connection further, using different populations and statistical methods. In one, researchers examined the health records of 388,254 children born in British Columbia, Canada, from 2000 to 2014. Because British Columbia has a central autism assessment network, the majority of children in the study went through the same screening and diagnostic process, which was not true for participants in the earlier studies.

About 1.5 percent of the Canadian children exposed to an epidural went on to be diagnosed with autism, compared with 1.3 percent of unexposed children, suggesting a small association.

But further analyses of the data weakened the finding. To control for some factors, such as maternal genetics and socioeconomic

status, for example, the researchers repeated the analysis in women who had multiple births, resulting in at least one child with autism and one without. The women were not more likely to have had an epidural while delivering the autistic child than the non-autistic one, they found.

Copenhagen University Hospital—Rigshospitalet in Denmark and lead investigator on the Danish study. “Personally, I would not have reservations about recommending a labor epidural to patients or family members seeking advice on labor pain management.”

**“There really is no solid evidence, from any of the studies actually, that epidural labor analgesia causes autism.”  
— Cynthia Wong**

#### MAKING ADJUSTMENTS:

In another study, researchers analyzed data from 479,178 children born in Denmark from 2006 through 2013. Unlike the other three studies, this analysis controlled for family history of autism and maternal psychiatric history, both of which are linked to an increased likelihood of autism. The researchers found no significant association between autism and epidurals.

“Assessing this link provides an excellent example of why confounders are almost always essential to address in an observational study,” says Anders Mikkelsen, an obstetrician and doctoral student at

All four studies also identified differences between parents who did and did not receive an epidural. For example, people who received an epidural tended to be younger and were more likely to have preeclampsia than those who didn’t—both factors linked to autism. And women who received an epidural were more likely to have a psychiatric condition, and their children were more likely to have a parent with autism. The differences suggest that none of the studies fully eliminated confounding factors, Wong wrote in the commentary.

“This is very complicated observational research

to do,” says Gillian Hanley, assistant professor of obstetrics and gynecology at the University of British Columbia and lead investigator on the new Canadian study. “Having multiple people do it, and do it slightly differently, and do it in different populations, and do it with different data, is valuable in the long run for getting us to the right answer to this question.”

Together, the studies are “reassuring” that epidurals are not associated with autism, Hanley says. Still, she says, researchers should attempt to work out which confounding factors lead to both use of epidural anesthesia and increased rates of autism diagnoses.

“We owe it to women to try to sort this out,” Hanley says.

[This story was originally published in September 2021.](#)

# As Cannabis Use Increases, Will Autism Rise as Well?

BY LAURA DATTARO

*A provocative study linked marijuana use during pregnancy to autism risk. Researchers say more evidence is needed.*

Women who use marijuana while pregnant may be more likely to give birth to an autistic child, according to a study published in *Nature Medicine*<sup>1</sup>.

The findings generated widespread press coverage, but researchers are calling for a cautious interpretation of the results—in part because the association surfaced through an analysis of birth records, not a controlled study.

“This is still a database study and it’s not going to answer all the questions,” says lead investigator Daniel Corsi, senior research associate at the Ottawa Hospital Research Institute in Canada. “We don’t have perfect data.”

The findings are “provocative,” particularly given the large study size, says Stephen Sheinkopf, associate professor of psychiatry and human behavior at Brown University in Providence, Rhode Island, who was not involved in the work.

Women are increasingly using marijuana during pregnancy, especially as more states in the United States and other countries legalize its use<sup>2</sup>. The trend has raised questions about how the substance affects fetal development.

But scientists need to take care in communicating the new results, Sheinkopf says: “These are going to be viewed not only by the public but also by policymakers.”



### MATCHING COHORTS:

The researchers tracked diagnoses of neurodevelopmental conditions, including autism, in more than 500,000 children born between 2007 and 2012 in Ontario, Canada. They used a birth registry to identify mothers who used cannabis during pregnancy. At a first trimester check-in, 0.6 percent of the mothers in the registry reported that they had.

Corsi and his colleagues also checked whether any of the children in the registry had been diagnosed with autism after age 18 months, or attention deficit hyperactivity disorder (ADHD), intellectual disability or learning disorders after age 4.

Of the half-million registered children, 7,125 were diagnosed with autism, the team found. And, Corsi says, the prevalence of autism was higher among children born to women who had used marijuana during pregnancy: 2.22 percent, compared with 1.41 percent among women who had not.

But marijuana users differed from nonusers in many other ways that could affect pregnancy outcomes: For example, they were far more likely to have a psychiatric condition, and to use other substances, such as alcohol and prescription drugs, during pregnancy.

To control for these potential confounding factors, the researchers pared down the non-user group—from nearly 500,000 to around 170,000—to match them to the user group more closely.

The association remained after the matching, Corsi says, with 2.45 percent of cannabis-exposed children receiving an autism diagnosis, compared with 1.46 percent of children who were not exposed. It also stood after controlling for other factors, such as examining women who used cannabis but no other substances.

“It’s compelling that their primary finding of that association with autism was able to be upheld,” says Rose Schrott, a doctoral candidate at Duke University in Durham, North Carolina, who was not involved in the research but has studied the effects of marijuana on autism genes<sup>3</sup>. The findings provide a “strong foundation” for additional, more tightly controlled studies, such as in animal models, she says.

### CAREFUL READING:

There are other confounding factors that the retrospective data can't capture, Corsi and others say.

For example, the information on a mother's psychiatric condition only captures her diagnosis, and does not take into account undiagnosed conditions or those in the father or other family members. Also, the socioeconomic status may be skewed because researchers measured it using census data on the area where the mothers lived, rather than individual household income.

And the data on marijuana use indicates only whether a mother used marijuana at all, not how much or often or whether for recreational or medicinal purposes—to treat nausea, for example. Demonstrating that more marijuana use leads to a stronger association with autism would strengthen the finding, says Keely Cheslack-Postava, research scientist at the New York State Psychiatric Institute in New York City, who was not involved in the research.

"It's a great use of the data that was there, but I would like to see that kind of evidence in the future to help us really assess if this is a true association," Cheslack-Postava says. As it stands, the study shows that the relationship between marijuana and autism is "a question that deserves further examination."

The study may underestimate marijuana use, Sheinkopf says, because mothers may be reluctant to report marijuana use during pregnancy due to stigma or concerns about legal repercussions.

"There's a long history of efforts to harshly criminalize drug use during pregnancy, and this is damaging to mothers and babies because it shunts women from the healthcare system to the legal system in really damaging ways," he says. "We as clinical scientists need to advocate for the findings to be used to improve healthcare and not for the purposes of criminalization of moms."

Future studies could examine cannabis use in a research setting, where privacy may be better protected than it is in a doctor's office. Corsi is also planning studies that use blood or urine samples to precisely measure cannabis levels during pregnancy.

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This article was originally published in 2020.

# The Link Between Vitamins, Supplements and Autism, Explained

BY PETER HESS

*Iron, vitamin D, folate and other nutrients are important to fetal health. How they affect the odds of autism is less clear.*



Prenatal vitamins help ensure that a fetus has everything it needs to develop. Research indicates that too little—or too much—of certain substances during pregnancy can increase the child’s chances of having autism.

But many of these studies are observational in nature and are not set up to prove a cause-and-effect relationship. In some cases, unrelated lifestyle factors—such as frequent hand-washing, eating a generally healthy diet, or other behaviors that are potentially more common among people who are thoughtful about prenatal nutrient intake—may explain an apparent link between prenatal nutrition and autism.

Here we explain what scientists know about the link between vitamin exposure, prenatal nutritional supplements and autism.

## *What is the connection between vitamin D and autism?*

Vitamin D is the nutrient whose connection to autism may be the most thoroughly studied. The relationship is modest, though, and the evidence only observational; it would be unethical to conduct clinical trials in which developing fetuses were deprived of vitamin D.

Giving pregnant women a low dose of halibut liver oil, which is rich in vitamin D, is linked to decreased rates of preeclampsia and preterm birth, according to a study conducted in London, England in the late 1930s. Both preeclampsia and preterm birth are linked to higher odds of autism.

More recent research, too, shows that having low levels of vitamin D during pregnancy is associated with a higher likelihood of having

a child with autism. Women with low blood levels of vitamin D during pregnancy, for example, were more than twice as likely to have a child with autism as those who were not vitamin D-deficient, according to one analysis in the Netherlands. But autism is relatively uncommon in this population—with a prevalence of 1.6 percent—so doubling the chances still represents only a small absolute increase over the 1.4 percent prevalence seen in the general population. Most of the women with low vitamin D did not have children with autism.

In the Dutch study, only low vitamin D levels during the second trimester were linked to autism odds. But vitamin D in the third trimester might also matter: Newborns with low blood levels of vitamin D were 33 percent more likely to later be diagnosed with autism than those born with high blood levels of vitamin D, according to a small study in Sweden.

Supplementing a woman's diet with vitamin D later in pregnancy does not seem to confer any benefit, though. Children whose mothers take high doses of vitamin D during the third trimester do not have a significantly different neurodevelopmental outcome early in life from that of controls, according to a randomized clinical trial.

Sunlight exposure enables the body to produce vitamin D, so some research has focused on autism prevalence among babies conceived during winter months, when there is less sunlight during the day. In one study in Scotland, 1.3 percent more children conceived during winter months had autism, intellectual disability or learning difficulties than did those conceived in sunnier seasons.

Some experts propose that the increased autism odds among children conceived during winter months are linked to the influenza season. Infections in pregnant women can lead to 'maternal immune

activation,' which, among other things, may speed up the expression of autism-linked genes.

#### *What about folate?*

Folic acid is the synthetic form of folate, a B vitamin, and is found in many prenatal supplements and fortified foods, such as cereals and pastas. It is crucial for cell proliferation, which is in overdrive during pregnancy. Insufficient folate during fetal development has long been linked to neural tube defects, such as spina bifida and anencephaly.

Multiple studies link prenatal folic acid supplementation to lowered odds of autism, even when pregnant women take epilepsy medications, such as valproic acid, that appear to increase those chances.

Too much folic acid may also increase the odds of autism, though. Excess folic acid supplementation had similar effects as folic acid deficiency in one mouse study, for example. The experimental mice in this study ingested 10 times as much folic acid as controls. These results do not mean folic acid should be avoided—just that it should be taken in recommended quantities.

#### *Is there evidence linking iron supplements with autism?*

This mineral is an essential component of the protein hemoglobin, which enables the blood to carry oxygen around the body and to a fetus' developing brain.

Anemia, or iron deficiency, during pregnancy is linked to increased odds of autism, intellectual disability and attention deficit hyperactivity disorder in children.

Iron may also offset any negative effects from maternal immune activation by protecting against a class of immune molecules called C-reactive proteins.

*Are there other nutritional factors at play—maybe fatty acids?*

Fatty acids reinforce cell membranes and ensure proper communication between neurons.

Some parents of autistic children swear by fish oil supplements to help ease behavioral issues, but the research is spotty.

Docosahexaenoic acid (DHA), an omega-3 fatty acid found in oily fish, may offset the effects of maternal malnutrition or stress, both of which can alter gene expression and contribute to autism odds, according to a mouse study.

Other fats may not have the same protective effects. A high-fat diet during pregnancy can lead to persistent, potentially harmful brain changes in mouse pups, according to one study. Some of the brain areas affected in this study include behavioral circuits associated with autism.

*What do you even do with this information?*

Half of pregnancies are unplanned, and in the case of some nutrients, such as folate, it is protective only if it's taken right before and just after conception. When it's best to take vitamin D is unclear, as is true for most other nutrients.

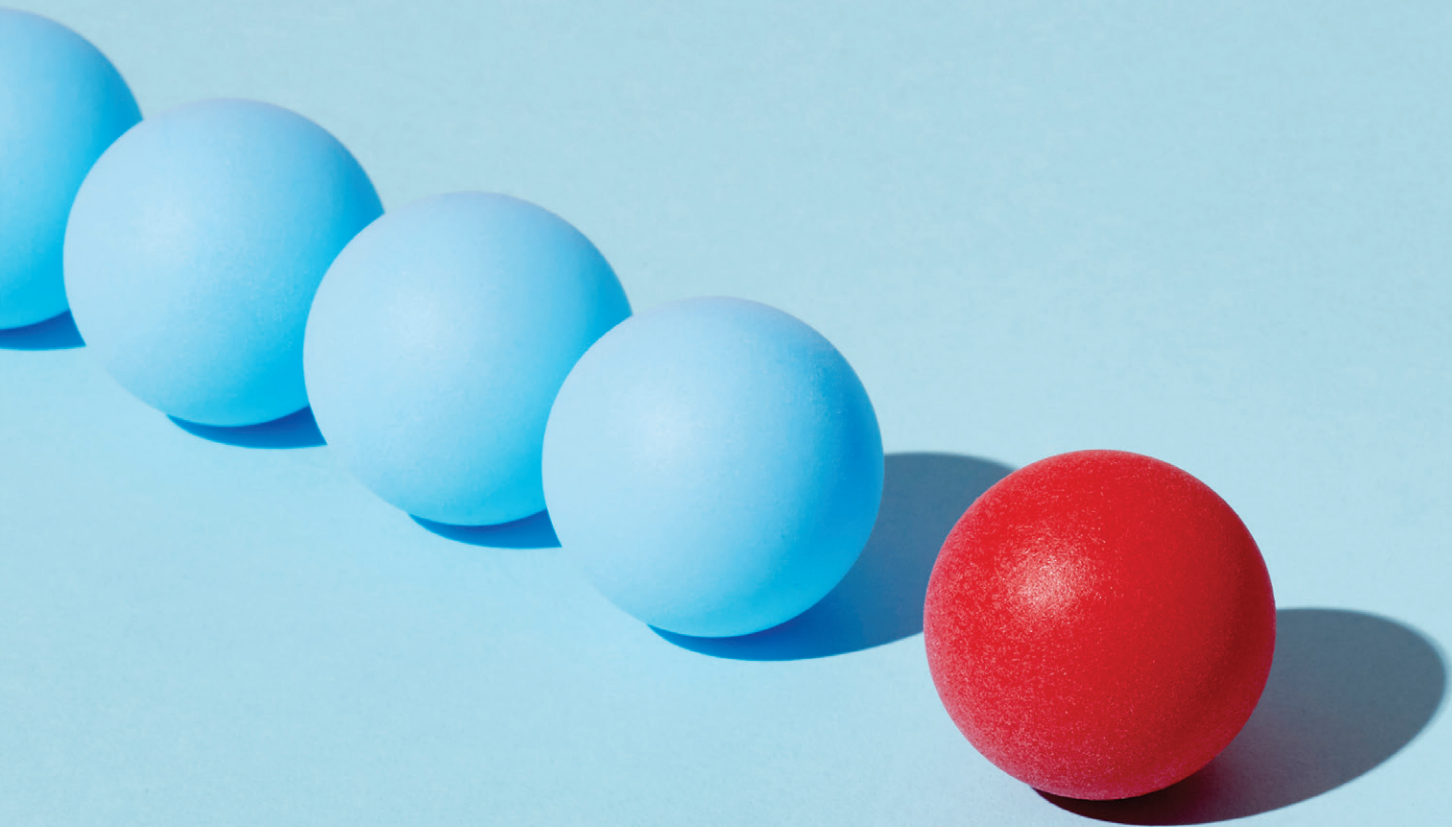
Additionally, many studies on prenatal nutrition contain a multitude of confounding or unmeasured variables. Scientists usually do everything they can to eliminate the impact of any confounding factor, such as maternal exercise, access to healthcare or a genetic predisposition, but it is not possible to eliminate every possibility. So any observational study on maternal nutrition and its link to autism comes with a big caveat: It cannot prove cause and effect.

Overall, there may be a non-causal association between prenatal vitamins and their protective effects. Research shows vitamins confer many benefits even when women take them for up to two years before getting pregnant: Women who take vitamins may be health-conscious in other ways.

Consulting with a physician is always best for each individual.

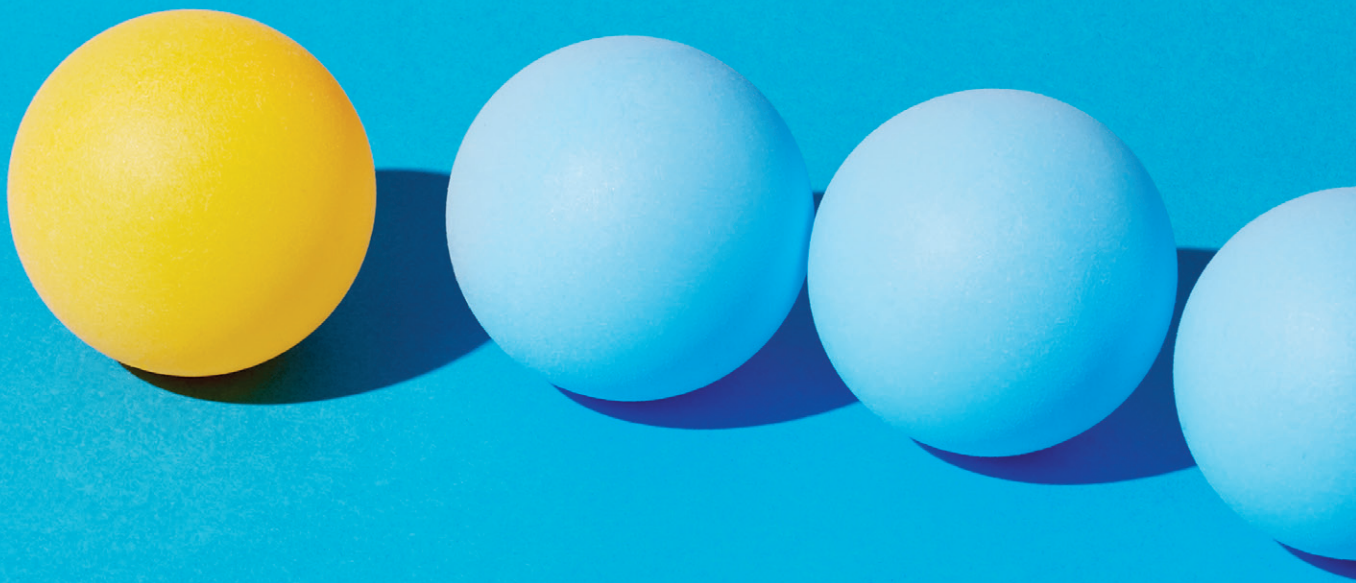
[This article was originally published in April 2021.](#)

*As cultures have evolved,  
their willingness and  
ability to measure socially  
defined conditions  
such as autism have  
changed as well.*



# IVV

## Changes in Society and Its View of Autism



# Being ‘Autistic While Black’ Can Mean Waiting Longer for a Diagnosis

BY LAURA DATTARO

*“There’s no doubt that African-American children are underserved and receive delayed interventions,” one expert says.*

Delays in autism diagnosis may contribute to the high rate of intellectual disability among Black autistic children in the United States, according to a study published in *Pediatrics*<sup>1</sup>.

Such delays mean these children miss out on age-appropriate, autism-specific care and a chance to improve their cognitive skills, the researchers say<sup>2</sup>.

“This is a very serious outcome, and we’re talking about very serious numbers of people affected by this,” says lead investigator John Constantino, professor of psychiatry and pediatrics at Washington University School of Medicine in St. Louis.

Until this year, data from the Centers for Disease Control and Prevention showed that a lower proportion of Black children were diagnosed with autism than were children of other races. A report published in March shows that gap has effectively closed<sup>3</sup>.

But other disparities remain: Among children with intellectual disability, Black children receive an autism diagnosis an average of six months later than white children, according to the March report. And 47 percent of Black autistic children also have intellectual disability, compared with 27 percent of white children.

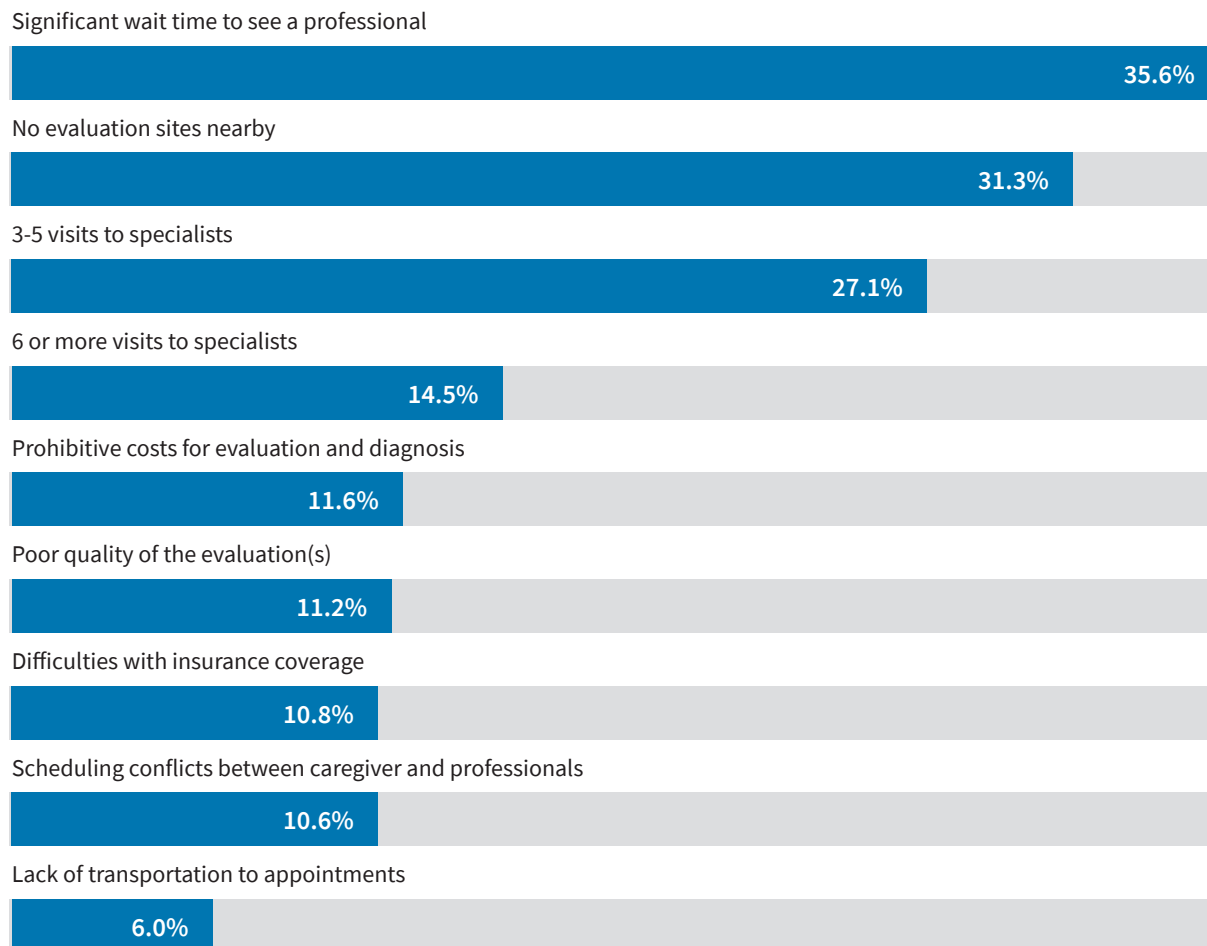
The new study is a “deep dive” on the role that access to services plays in this disparity, Constantino says.

“We can’t just sit with that if we don’t at least try to see whether some of this can be resolved by leveling the playing field for diagnosis and access to services,” he says. “There’s almost no excuse.”



## OBSTACLES TO AUTISM DIAGNOSES FOR BLACK FAMILIES

When asked about their children’s autism diagnoses, Black families describe various delays and barriers:



The researchers surveyed 517 families of 584 Black autistic children across four sites in the United States.

### LONG DELAYS:

The researchers examined the experiences of Black families in the U.S. as they sought a diagnosis and treatment for concerns about a child’s development, language or behavior.

They interviewed the parents of 584 Black children with autism, including 118 girls, and compiled timelines of the families’ experiences, including

the developmental outcomes of the autistic children and their siblings.

They found a three-year delay in diagnosis: On average, parents first noted concerns about their child’s development when the child was 23 months old and told a professional six months later, but didn’t receive an autism diagnosis until their child was more than 5 years old.

*“Many minority children also aren’t screened until they start school . . . We’re missing a window that we could intervene or improve,” Zeleke says.*

More than a third of the families reported long wait times to see a professional; 14 percent made at least six visits to specialists before their child was diagnosed. Nearly a third said that a lack of available professionals contributed to the diagnostic delay.

The study found no links between the autistic children’s intelligence quotient (IQ) and their family’s income or parents’ education, meaning the increased prevalence of intellectual disability among Black autistic children can’t be attributed to poverty, Constantino says. Poverty, which disproportionately affects Black families in the U.S, is associated with worse cognitive outcomes.

“A simple sort of excuse of saying, ‘Well, that’s the problem of poverty, we can’t fix that,’ is inappropriate,” Constantino says.

There was also no association with gestational age at birth or the extent to which IQ varies among the child’s immediate family members, both of which are linked to low IQ in the general population.

Instead, the results suggest that a lack of access to services at the right time may hold these children back, Constantino says. The study found that the autistic children began receiving some kind of care one to three years prior to an autism diagnosis, suggesting they did not benefit from autism-specific therapies.

The findings serve as a call to action for the research community, says Walter Zahorodny, associate professor of pediatrics at Rutgers New Jersey Medical School in Newark, who was not involved in the work.

“There’s no doubt that African-American children are underserved and receive delayed interventions,” Zahorodny says. “Certainly, that’s something that deserves respect and action.”

#### UNEQUAL ENVIRONMENT:

It’s not clear from the findings that diagnostic delays underlie the increased prevalence of intellectual disability in Black autistic children, other researchers say—particularly given that the CDC’s report shows only a six-month age gap in diagnosis between Black and white children.

“While it’s possible, it also seems speculative,” Zahorodny says. “I don’t think it’s proven that six months’ earlier intervention could make a difference in the intellectual capacity of a child. That’s a stretch, I think.”

Other factors linked to low IQ could also contribute to the disparity, including lead poisoning and quality of nursery schools, says Maureen Durkin, professor of public health at the University of Wisconsin-Madison, who was not involved in the research. Some families have reported difficulty getting therapists to visit their homes if they live in a neighborhood perceived as “dangerous,” she says.

“We do need to address all of those,” Durkin says. “I think it’s important to draw attention to this.”

Future research should tease out what creates the environment for racial disparities in care to persist, says Waganesh Zeleke, associate professor of clinical mental health counseling at Duquesne University in Pittsburgh, who was not involved in the research. Zeleke’s research has shown that white families of autistic children say they are more satisfied with the healthcare they receive and more likely to contact a professional about concerns than minority families are<sup>4</sup>.

Many minority children also aren’t screened until they start school, Zeleke says, further delaying the process.

“We’re missing a window that we could intervene or improve,” Zeleke says. “I am glad they pointed it out, named it and addressed it directly. It’s a wakeup call for interventionists to see it and name it for what it is.”

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# LATINO CHILDREN IN THE UNITED STATES HAVE A HARDER TIME GETTING EVALUATED FOR AUTISM

BY KRISTINA LOPEZ

*Social workers can help reduce the structural inequalities that create these and other health disparities.*

Autism can affect anyone, and yet there are stark disparities in how children of different races, ethnicities and income level are diagnosed and treated<sup>1</sup>.

Latino children are often overlooked in the United States. They comprise one-fourth of all children in the country under age 18 and are expected to make up one-third by 2050. However, U.S. prevalence data have consistently shown that fewer Latino children than white or Black children are diagnosed with autism<sup>2</sup>. Other research indicates that Latino children tend to be diagnosed later than white children<sup>3</sup>.

These findings are concerning, given the importance of identifying autism early and intervening to enhance a child's social-communication skills. Researchers and clinicians need to consider the cultural factors that may influence autism diagnosis and treatment, develop new assessment tools and programs dedicated to the Latino population, and explore other means to lower the disparities.

My colleagues and I propose that much of the difference in autism prevalence between Latino and white children stems from structural inequalities within the education and healthcare systems. But social workers are in a prime position to help identify and support Latino children with autism<sup>4</sup>. Because they often serve children from low-income or ethnic minority groups, they have ample opportunity to enhance autism diagnosis and treatment for Latino children—especially when they are trained in antiracist practices and cultural humility.

## AREAS OF OPPORTUNITY:

We reviewed the literature on Latino children and autism and identified three main areas of opportunity for social workers to address disparities in autism diagnosis and treatment.

The first pertains to those who work directly with individual Latino children and families. We urge these social workers to learn about autism and cultural humility, or the ability to be aware of one's own cultural values and biases and to reflect on how that perspective shapes one's worldview. Although social workers are trained to be cognizant of people's differences in race, ethnicity, income, gender and ability, few have training on autism or its intersection with cultural factors. Including this information in training courses for social workers can help them to better identify Latino children who may have autism, and to provide these families with information and community resources.

Other opportunities for improvement relate to social workers at institutions such as schools and hospitals, and at organizations focused on crafting new policies. We suggest that these social workers incorporate Latina and Latino Critical Race Theory, or 'LatCrit,' into their practice. LatCrit is a theoretical framework to help people recognize the oppression and discrimination the Latino community encounters. To practice LatCrit, social workers learn to explore their own biases about the Latino community, learn about the history of oppression in the Latino community and learn how to recognize the community's strengths that can be built upon and embedded in a culturally responsive practice, to collaborate with community agencies that serve the Latino population and to actively recruit more Latino individuals into the social-work profession.

With these areas of opportunity in mind, we developed Parents Taking Action (PTA), an education program for Latino families of children with autism. To create PTA, we adapted existing information about autism diagnosis, treatments and services for the Latino community. We trained Latina community health workers, or 'promotoras,' who themselves are mothers of autistic children, to deliver information about autism to other Latina mothers. This includes information about advocacy strategies, evidence-based techniques to enhance children's social

communication and self-care strategies. We provided some information in the form of audio-recorded novelas, or short stories, narrated by actors, to make it more culturally relevant.

We know this approach can work. We tested PTA in a study involving 96 Latino families with an autistic child<sup>5</sup>. Half of these families received PTA training in their homes and in their preferred language over the course of 14 weeks. Compared with controls, children in families that got the intervention received more evidence-based services. And Latina mothers in these families showed an increase in their use of social-communication intervention strategies with their children.

We challenge all social workers to be strategic in incorporating culturally relevant frameworks into their research and practice. In so doing, social workers can help dismantle the forces that limit Latino children's access to autism diagnosis and treatment services.

*Kristina Lopez is assistant professor of social work at Arizona State University in Phoenix.*

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# WHAT HAPPENS WHEN A TODDLER SCREENS POSITIVE FOR AUTISM?

BY PETER HESS

*In most cases, the answer is: too little.  
Many pediatricians are still failing to send children  
under their care for the appropriate evaluations.*

Most toddlers who screen positive for autism do not receive the recommended referrals for follow-up tests and therapies, a new study of nearly 4,500 children suggests<sup>1</sup>.

The American Academy of Pediatrics recommends that doctors screen all children for autism starting at 18 months of age and refer children with positive test results to an autism specialist for further evaluation, to an audiologist for a hearing test and to early-intervention services for therapy<sup>2</sup>.

Those three referrals happen for only about 4 percent of children flagged by a popular autism screening tool during routine doctor visits, the new work shows.

“What this study shows is that people are not following [autism screening guidelines], at least with regard to referral-making,” says Katharine Zuckerman, associate professor of pediatrics at Oregon Health and Science University in Portland, who was not involved in the study. “It doesn’t matter if you screen everybody if you don’t refer anybody when you have a positive screening-test result.”

Doctors appear to refer only some children for some services, depending on the child’s sex, race and other characteristics, says co-lead researcher Kate Wallis, developmental behavioral pediatrician at Children’s Hospital of Philadelphia in Pennsylvania. For example, her team found that clinicians are less likely to refer girls than boys for early intervention.

“We have to find ways to improve referral rates so that all children can be evaluated and begin in therapy services,” Wallis says.

## CLINICAL CONSIDERATIONS:

Wallis and her colleagues analyzed electronic health records from routine visits to 31 primary care clinics in Pennsylvania and New Jersey from 2013 to 2016. Doctors at these clinics screen all toddlers for autism when they are 16 to 30 months old, using a standardized questionnaire for parents called the Modified Checklist for Autism in Toddlers (M-CHAT). Doctors are supposed to do a follow-up interview with the parents of any child whose scores indicate a “moderate risk” and then decide whether the child has screened positive or negative.

The researchers found 4,442 children whose M-CHAT scores warranted a follow-up interview with their parents. But that interview took place for less than half of them, or 1,660 children. Doctors did not do an interview for 63 percent of children, including 473 who scored so high that no interview was needed to confirm the results.

Of the children whose parents had follow-up interviews, doctors determined that 1,560, or 94 percent, had screened negative. This may indicate that clinicians do follow-ups mainly when they suspect false positives. False positives are a known issue with the M-CHAT, and the follow-up interview is designed to weed them out.

Families with public insurance were among the most likely to receive a follow-up interview. Clinicians may be more likely to refer children for a follow-up interview when they know a family’s insurance will cover it — as most public insurance does, the researchers say. The findings were published in *PLOS One*.

The results highlight a need to understand what drives decision-making after a positive autism screen, Wallis says. “Some pediatricians may not trust the results of the screen, they may have other competing health priorities to address during the visit, or they may not want to worry parents if they are unsure if a child has [autism].”

## ADDRESSING DISPARITIES:

The team further analyzed the referrals for 2,882 children with a positive screen: About 11 percent were referred to specialists for a comprehensive autism evaluation, and about 11 percent were referred to an audiologist.

Around 31 percent were referred to early-intervention services; another 26 percent were already receiving early interventions.

The study shows that some underserved groups benefit in some ways from universal autism screening, says Tiffany Baffour, associate professor of social work at the University of Utah in Salt Lake City, who was not involved in the study. For instance, Black children were more likely than white children to be referred to an audiologist, though they were less likely to be referred for early intervention.

But some families referred for early intervention or further screening refused to follow up, which raises new questions, Baffour says. To increase the value of universal screening, researchers need to identify the barriers, such as transportation or finances, that keep some families from referrals.

Wallis' team plans to examine whether disparities in referrals after screening skew autism diagnosis and prevalence rates. To increase the number of pediatricians following clinical guidelines, they also plan to look at how clinicians make decisions about referrals for evaluation and treatment after a positive screening.

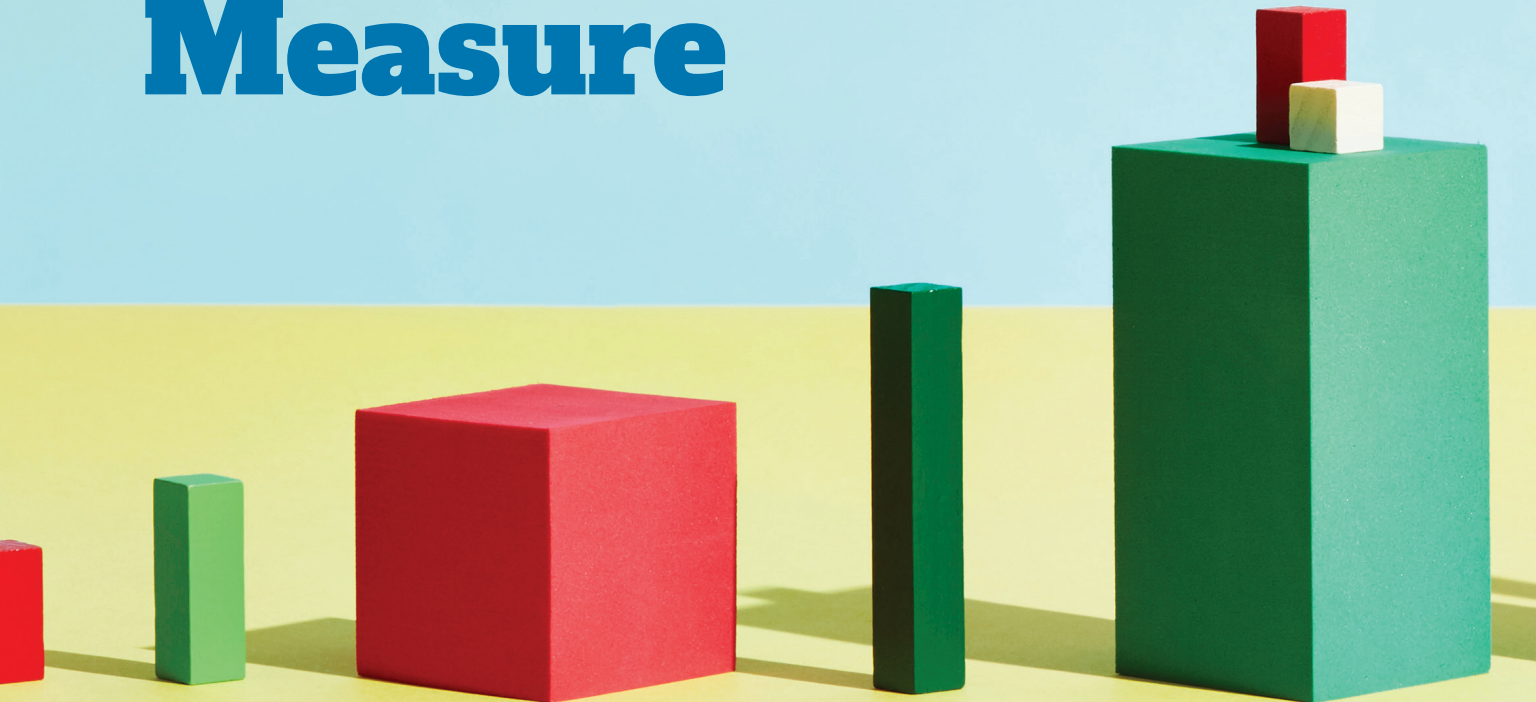
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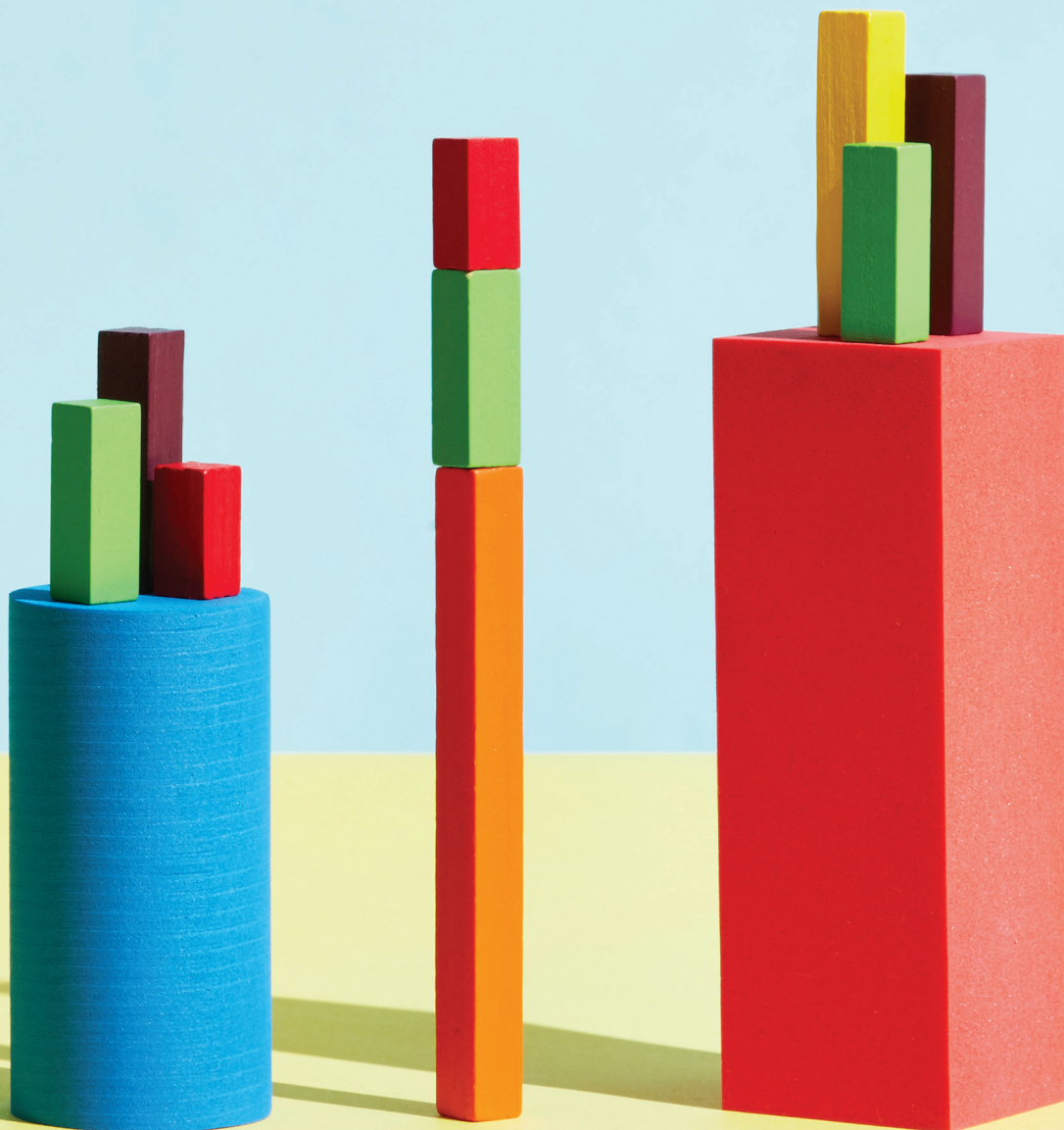
# V

## Challenges in Taking Autism's Measure





*How many autistic people are there? The diagnostic and statistical tools needed to answer that question definitively are still not there.*



# The Evolution of ‘Autism’ as a Diagnosis, Explained

BY LINA ZELDOVICH

*From childhood schizophrenia and ‘refrigerator mothers’ to shifting diagnostic criteria, psychiatry has struggled to define autism in a formal way that meets the needs of the community.*



You can draw a straight line from the initial descriptions of many conditions—claustrophobia, for example, or vertigo - to their diagnostic criteria. Not so with autism. Its history has taken a less direct path with several detours, according to Jeffrey Baker, professor of pediatrics and history at Duke University in Durham, North Carolina.

Autism was originally described as a form of childhood schizophrenia and the result of cold parenting, then as a set of related developmental disorders, and finally as a spectrum condition with wide-ranging degrees of impairment. Along with these shifting views, its diagnostic criteria have changed as well.

Here is how the “Diagnostic and Statistical Manual of Mental Disorders” (DSM), the diagnostic manual used in the United States, has reflected our evolving understanding of autism.

## *Why was autism initially considered a psychiatric condition?*

When Leo Kanner, an Austrian-American psychiatrist and physician, first described autism in 1943, he wrote about children with “extreme autistic aloneness,” “delayed echolalia” and an “anxiously obsessive desire for the maintenance of sameness.” He also noted that the children were often intelligent and some had extraordinary memory.

As a result, Kanner viewed autism as a profound emotional disturbance that does not affect cognition. In keeping with his perspective, the second edition of the DSM, the DSM-II, published in 1952, defined autism as a psychiatric condition—a form of childhood schizophrenia marked by a detachment from reality. During the 1950s and 1960s, autism was thought to be rooted in cold and unemo-

tional mothers, whom Bruno Bettelheim dubbed ‘refrigerator mothers.’

### *When was autism recognized as a developmental disorder?*

The ‘refrigerator mother’ concept was disproved in the 1960s to 1970s, as a growing body of research showed that autism has biological underpinnings and is rooted in brain development. The DSM-III, published in 1980, established autism as its own separate diagnosis and described it as a “pervasive developmental disorder” distinct from schizophrenia.

Prior versions of the manual left many aspects of the diagnostic process open to clinicians’ observations and interpretations, but the DSM-III listed specific criteria required for a diagnosis. It defined three essential features of autism: a lack of interest in people, severe impairments in communication and bizarre responses to the environment, all developing in the first 30 months of life.

### *How long did this definition last?*

The DSM-III was revised in 1987, significantly altering the autism criteria. It broadened the concept of autism by adding a diagnosis at the mild end of the spectrum—pervasive developmental disorder-not otherwise specified (PDD-NOS)—and dropping the requirement for onset before 30 months.

Even though the manual did not use the word ‘spectrum,’ the change reflected the growing understanding among researchers that autism is not a single condition but rather a spectrum of conditions that can present throughout life.

The updated manual listed 16 criteria across the three previously established domains, 8 of which had to be met for a diagnosis. Adding PDD-NOS allowed clinicians to include children who didn’t

fully meet the criteria for autism but still required developmental or behavioral support.

### *When was autism first presented as a spectrum of conditions?*

The DSM-IV, released in 1994 and revised in 2000, was the first edition to categorize autism as a spectrum.

This version listed five conditions with distinct features. In addition to autism and PDD-NOS, it added ‘Asperger’s disorder,’ also at the mild end of the spectrum; ‘childhood disintegrative disorder (CDD),’ characterized by severe developmental reversals and regressions; and Rett syndrome, affecting movement and communication, primarily in girls. The breakdown echoed the research hypothesis at the time that autism is rooted in genetics, and that each category would ultimately be linked to a set of specific problems and treatments.

### *Why did the DSM-5 adopt the idea of a continuous spectrum?*

Throughout the 1990s, researchers hoped to identify genes that contribute to autism. After the Human Genome Project was completed in 2003, many studies tried to zero in on a list of ‘autism genes.’ They found hundreds, but could not link any exclusively to autism. It became clear that finding genetic underpinnings and corresponding treatments for the five conditions specified in the DSM-IV wouldn’t be possible. Experts decided it would be best to characterize autism as an all-inclusive diagnosis, ranging from mild to severe.

At the same time, there was growing concern about a lack of consistency in how clinicians in different states and clinics arrived at a diagnosis of autism, Asperger syndrome or PDD-NOS. A spike in

autism prevalence in the 2000s suggested that clinicians were sometimes swayed by parents lobbying for a particular diagnosis or influenced by the services available within their state.

To address both concerns, the DSM-5 introduced the term ‘autism spectrum disorder.’ This diagnosis is characterized by two groups of features: “persistent impairment in reciprocal social communication and social interaction” and “restricted, repetitive patterns of behavior,” both present in early childhood. Each group includes specific behaviors, a certain number of which clinicians have to identify. The manual eliminated Asperger syndrome, PDD-NOS and classic autism, but debuted a diagnosis of social communication disorder to include children with only language and social impairments. Childhood disintegrative disorder and Rett syndrome were removed from the autism category.

#### *Why did the DSM-5 spawn so much concern and controversy?*

Even before the manual was released in 2013, many people with autism and their caregivers worried about its effect on their lives. Many were concerned that after their diagnosis disappeared from the book, they would lose services or insurance coverage. Those who identified themselves as having Asperger syndrome said the diagnosis gave them a sense of belonging and an explanation for their challenges; they feared that removing the diagnosis was synonymous to losing their identity. And experts disagreed on whether the DSM-5’s more stringent diagnostic criteria would block services for those with milder traits or adequately curb surging prevalence rates.

Five years later, it’s clear the DSM-5 did not cut services for people already diagnosed with an

autism spectrum condition. A growing body of evidence, however, shows that its criteria do exclude more people with milder traits, girls and older individuals than the DSM-IV did.

#### *Are there alternatives to the DSM?*

Clinicians in many countries, including the United Kingdom, use the International Classification of Diseases. Released in the 1990s, that manual’s current and 10th edition groups autism, Asperger syndrome, Rett syndrome, CDD and PDD-NOS together in a single ‘Pervasive Developmental Disorders’ section, much as the DSM-IV did.

#### *What does the future look like for diagnosing autism?*

Experts continue to view autism as a continuous spectrum of conditions. There are no planned revisions to the DSM for now, but the language in a draft of the ICD-11—which is expected to debut in May 2018—mirrors the DSM-5’s criteria. In the ICD-11, autism criteria move to a new, dedicated ‘Autism Spectrum Disorder’ section.

The ICD-11 differs from the DSM-5 in several key ways. Instead of requiring a set number or combination of features for a diagnosis, it lists identifying features and lets clinicians decide whether an individual’s traits match up. Because the ICD is intended for global use, it also sets broader, less culturally specific criteria than the DSM-5 does. For instance, it puts less emphasis on what games children play than whether they follow or impose strict rules on those games. The ICD-11 also makes a distinction between autism with and without intellectual disability, and highlights the fact that older individuals and women sometimes mask their autism traits.

[This article was originally published in 2018.](#)

# Can a Computer Diagnose Autism?

BY JEREMY HSU

*Machine-learning holds the potential to help clinicians spot autism sooner, but technical and ethical obstacles remain.*

Martin Styner's son Max was 6 by the time clinicians diagnosed him with autism. The previous year, Max's kindergarten teacher had noticed some behavioral signs. For example, the little boy would immerse himself in books so completely that he shut out what was going on around him. But it wasn't until Max started to ignore his teacher the following year that his parents enlisted the help of a child psychologist to evaluate him.

Max is at the mild end of the spectrum. Even so, Styner, associate professor of psychiatry and computer science at the University of North Carolina at Chapel Hill, wondered if he had been fooling himself by not seeing the signs earlier. After all, Styner has studied autism for much of his career.

Given how complex and varied autism is, it's not surprising that even experts like Styner don't always recognize it right away. And even when they do spot the signs, getting an autism diagnosis takes time: Families must sometimes visit the nearest autism clinic for several face-to-face appointments. Not everyone has easy access to these clinics, and people may wait months for an appointment.

That reality has led to a detection gap: Although an accurate diagnosis can be made as early as 2 years of age, the average age of diagnosis in the United States is 4. And yet the earlier the diagnosis, the better the outcome.

Some researchers say delays in autism diagnosis could shrink with the rise of machine learning—a technology developed as part of artificial-intelligence research. In particular, they are pinning their hopes on the latest version of machine learning, known as deep learning. “Machine learning was always a part of the field,” Styner



says, “but the methods and applications were never strong enough to actually have clinical impact; that changed with the onset of deep learning.”

Deep learning’s power comes from finding subtle patterns, among combinations of features, that might not seem relevant or obvious to the human eye. That means it’s well suited to making sense of autism’s heterogeneous nature, Styner says. Where human intuition and statistical analyses might search for a single, possibly nonexistent trait that consistently differentiates all children with autism from those without, deep-learning algorithms look instead for clusters of differences.

Still, these algorithms depend heavily on human input. To learn new tasks, they ‘train’ on datasets that typically include hundreds or thousands of ‘right’ and ‘wrong’ examples—say, a child smiling or not smiling—manually labeled by people. Through intensive training, though, deep-learning applications in other fields have eventually matched the accuracy of human experts. In some cases, they have ultimately done better.

“I think these approaches are going to be reliable, quantitative, scalable—and they’re just going to reveal new patterns and information about autism that I think we were just unaware of before,” says Geraldine Dawson, professor of psychiatry and behavioral sciences at Duke University in Durham, North Carolina. Not only will machine learning help clinicians screen children earlier, she says, but the algorithms might also offer clues about treatments.

Not everyone is bullish on the approach’s promise, however. Many experts note that there are technical and ethical obstacles these tools are unlikely to surmount any time soon. Deep learning—and machine learning, more broadly—is not a “magic wand,” says Shrikanth Narayanan, pro-

fessor of electrical engineering and computer science at the University of Southern California in Los Angeles. When it comes to making a diagnosis and the chance that a computer might err, there are “profound implications,” he says, for children with autism and their families. But he shares the optimism many in the field express that the technique could pull together autism research on genetics, brain imaging and clinical observations. “Across the spectrum,” he says, “the potential is enormous.”

#### BIGGER IS BETTER:

To make accurate predictions, machine-learning algorithms need vast amounts of training data. That requirement presents a serious challenge in autism research because most data relevant to diagnoses comes from painstaking—and therefore limited—clinical observations. Some researchers are starting to build larger datasets using mobile devices with cameras or wearable sensors to track behaviors and physiological signals, such as limb movements and gaze.

In 2016, a European effort called the DE-ENIGMA project started building the first freely available, large-scale database based on the behaviors of 62 British and 66 Serbian children with autism. So far, this dataset includes 152 hours of video interactions between the children and either adults or robots. “One of the primary goals of the project is to create a database where you can train machine learning to recognize emotion and expression,” says Jie Shen, a computer scientist at Imperial College London and DE-ENIGMA’s machine-learning expert.

Dawson’s team at Duke is also collecting videos of children with autism via a mobile app developed for a project called Autism & Beyond. During the project’s initial year-long run in 2017, more than

1,700 families took part, uploading nearly 4,500 videos of their children’s behaviors and answering questionnaires. “We were getting in a year the amount of data that experts might get in a lifetime,” says Guillermo Sapiro, professor of electrical and computer engineering at Duke, who is working on the app’s next iteration.

The group is also training a deep-learning algorithm to interpret the actions in the video clips and detect specific behaviors—something Dawson describes as ‘digital phenotyping.’ At this year’s meeting of the International Society for Autism Research, Dawson presented results from a study of 104 toddlers, including 22 with autism, who watched a series of videos on a tablet. The tablet’s camera recorded the child’s facial expressions and head movements. The algorithm picked up on a two-second delay in the autistic children’s response to someone calling their name. Clinicians could easily miss this slight lag, an important red flag for autism, Dawson says.

One caveat to this kind of an approach is that collecting data outside the structured confines of a lab or doctor’s office can be messy. Sapiro says he was puzzled by the algorithm’s assessment of one participant in the Autism & Beyond project, who showed a mix of developmentally typical and atypical behaviors. When Sapiro watched the videos of that little girl, though, he quickly realized what was going on: Her behavior was typical during the day but atypical at night, when she was tired.

Researchers might be able to interpret these videos more readily by combining them with information from sensors capturing a child’s behavior. A group of scientists at the Georgia Institute of Technology in Atlanta is exploring this approach, which they describe as ‘behavioral imaging.’ One of

the scientists, Gregory Abowd, has two sons on the spectrum. “My oldest is a non-speaking individual, and my younger one speaks but has difficulty with communicating effectively,” Abowd says. In 2002, three years after his oldest son was diagnosed with autism at age 2, he says, “I started to get interested in what I could do as a computer scientist to address any of the challenges related to autism.”

The Georgia Tech scientists are investigating sensors to track a range of physiological and behavioral data. In one project, they are using wearable accelerometers to monitor physical movements that could signify problem behaviors, such as self-injury. Another initiative involves glasses fitted with a camera located on the bridge of the nose to make it easier to follow a child’s gaze during play sessions.

The dream, says computer scientist James Rehg, is to train machine-learning algorithms to use these signals to automatically generate a snapshot of a child’s resulting social-communication skills. “I think it’s a really exciting time and an exciting area precisely because of the wealth of signals and different kinds of information that people are exploring,” says Rehg.

Comprehensive behavioral data could also yield clues about conditions that often co-occur with autism, says Helen Egger, chair of the child and adolescent psychiatry at NYU Langone Health in New York City and co-investigator on the Autism & Beyond project. Egger says larger datasets may help make sense of the overlap in behavioral traits between autism and conditions such as anxiety, attention deficit hyperactivity disorder, obsessive-compulsive disorder and depression. “We have to be able to use these tools with the full spectrum of children to differentiate children with

autism from those without autism,” she says.

#### THE EARLIEST SIGNALS:

Some research teams hope to train machine-learning models to detect signs of autism even before behavioral symptoms emerge.

Styner and his colleagues in the Infant Brain Imaging Study (IBIS), a research network across four sites in the U.S., are using deep learning to analyze the brain scans of more than 300 baby siblings of children with autism. Because these ‘baby sibs’ are known to be at an increased risk of autism, it might be easier to spot signs of the condition in this group. In 2017, IBIS published two studies in which machine-learning algorithms picked up on certain patterns in brain growth and wiring and correctly predicted an autism diagnosis more than 80 percent of the time.

“One key difference between our studies and many machine-learning studies is that ours have been predicting later diagnostic outcome from a pre-symptomatic period,” says Joseph Piven, professor of psychiatry and director of the Carolina Institute for Developmental Disabilities at the University of North Carolina at Chapel Hill and an IBIS investigator. “That will clearly be useful clinically, if replicated.”

Machine learning trained on brain imaging might also provide more than a binary ‘yes’ or ‘no’ prediction about a diagnosis, Styner says. It could also forecast where that child falls along on the autism spectrum, from mild to severe. “That’s what we’re heading for, and I see in our research and in other people’s research that that’s definitely possible,” he says.

One factor limits the volume of brain-imaging data that can be collected: Participants have to find



magnetic resonance imaging machines, which are bulky, expensive and tricky to use with children. A more flexible option for detecting early signs of autism may be electroencephalography (EEG), which monitors electrical activity in the brain via portable caps studded with sensors. “It was and still is the only brain measurement tech that can be used widely in clinical care practice,” says William

Even when they are promising, algorithms reveal nothing about the biological significance of their predictive findings, researchers caution. “We don’t know what the computer is picking up in the EEG signal per se,” says Charles Nelson, director of research at Boston Children’s Hospital’s Developmental Medicine Center, who co-led the EEG work. “Maybe it is a good predictive biomarker, and as a

## **Even when they are promising, algorithms reveal nothing about the biological significance of their predictive findings.**

Bosl, associate professor of health informatics, data science and clinical psychology at the University of San Francisco.

Machine-learning algorithms represent just the first part of the equation in working with EEG. The second involves what Bosl describes as the “secret sauce”—additional computer methods that remove noise from these signals and make it easier to detect patterns in the data. In a 2018 study, Bosl and his colleagues used this algorithmic mix to monitor the EEGs of 99 baby sibs and 89 low-risk infants for almost three years. Using EEG data from babies as young as 3 months, the method was able to predict severity scores on the gold-standard diagnostic test, the Autism Diagnostic Observation Schedule (ADOS).

result we can make a later prediction about a later outcome, but it doesn’t tell us why children develop autism.”

Like researchers working with brain imaging or behavioral data, those focused on EEG are also relying on relatively small datasets, which comes with complications. For example, sometimes an algorithm learns the patterns of a particular dataset so well that it cannot generalize what it has learned to larger, more complex datasets, Bosl says. This problem, called ‘overfitting,’ makes it especially important for other studies—ideally by independent teams—to validate results.

Another common pitfall arises when researchers use training datasets that contain an equal number of children with and without autism,

Styner says. Autism is not present in half of all children; it's closer to 1 in 60 children in the U.S. So when the algorithm moves from training data to the real world, its 'needle-in-a-haystack' problem—identifying children with autism—becomes far more challenging: Instead of finding 100 needles mixed in with 100 strands of hay, it must find 100 needles mixed in with 6,000 strands of hay.

The company offers telemedicine solutions, such as the Naturalistic Observation Diagnostic Assessment app, which allows clinicians to make remote autism diagnoses based on uploaded home videos.

Behavior Imaging is partway through a study that aims to train machine-learning algorithms to characterize behaviors in videos of children. Once they identify the behaviors, they could draw cli-

**“By and large, I think the biggest problem we have is people with data-mining expertise going to datasets they don’t comprehend. . . .”**  
**—Fred Shic**

#### COMPUTER ASSIST:

Given these challenges, many autism researchers remain hesitant about rushing to commercialize applications based on machine learning. But a few have more willingly engaged with startups—or launched their own—with the goal of bypassing the autism-screening bottleneck.

Abowd has served as chief research officer for a Boise, Idaho-based company called Behavior Imaging since 2005, when Ron and Sharon Oberleitner founded the company, almost a decade after their son was diagnosed with autism at age 3.

nicians’ attention to those key timestamps in the video and spare them from having to watch the video from start to finish. In turn, clinicians could improve the algorithm by either confirming or correcting its assessments of those moments. “This is going to be a clinical-decision-support tool that is going to constantly build up the industry expertise of what atypical behaviors of autism actually are,” Ron Oberleitner says.

A more ambitious vision for computer-assisted autism screening comes from Cognoa, a startup based in Palo Alto, California. The company offers

a mobile app that provides risk assessments to parents based on roughly 25 multiple-choice questions and videos of their child's activities. Ultimately, Cognoa's leaders want U.S. Food and Drug Administration approval for an application that they say will empower pediatricians to diagnose autism and refer children directly for treatment.

Dennis Wall, now a researcher at Stanford University, founded Cognoa in 2013. After two studies published in 2012, he says, he became convinced that his machine-learning algorithms could be trained to make autism diagnoses more accurately and faster than two screening tools, the ADOS and the Autism Diagnostic Interview-Revised (ADI-R). "It was a solid step forward and provided a sound launch pad for future work," Wall says.

But Wall's 2012 papers didn't convince everyone. Several critics, including Narayanan, pointed out in a 2015 analysis that the studies used small datasets and only considered children with severe autism, excluding the most complicated and difficult-to-diagnose forms of the condition. In the real world, they argued, his algorithms would miss many diagnoses a clinician would catch. Wall published a 2014 validation study that he says upheld the algorithm's performance on an independent dataset, including data from children in the middle of the spectrum. He acknowledges that the 2012 studies used smaller datasets, but says the accuracy of his algorithms holds up in larger datasets used in later studies.

In 2016, Narayanan and some of his 2015 co-investigators described their own efforts to use machine learning to streamline autism screening and diagnosis. In their conclusion, they sounded a note of caution, saying that their algorithms, trained on responses from parents

seeking a diagnosis for their child, also performed well but needed more testing in larger and more diverse populations. "I feel that there is a clear potential to fine-tune associated clinical-instrument algorithms with machine learning," says co-investigator Daniel Bone, senior scientist at Yomdle, Inc., a technology startup based in Los Angeles and Washington, D.C. "However, I've not seen clear evidence yet—my own work included—that this approach is a monumental step beyond the traditional statistical methods that have been employed by researchers for decades."

Merely amassing data to train machine-learning algorithms won't necessarily help, says Bone's collaborator, Catherine Lord, director of the Center for Autism and the Developing Brain in White Plains, New York, who developed the ADOS. Sometimes there are obvious but unacknowledged explanations for an algorithm's apparent success, Lord adds. For example, boys are diagnosed with autism about four times more often than girls. A machine-learning study that appears to succeed in predicting the difference between people with and without autism may in fact be noticing nothing more than gender differences. Likewise, it might be picking up on differences in intelligence. "It isn't the machine learning's fault," Lord says. "It's the human reviewers and the general idea that if you have enough study subjects you can do anything."

#### ARE WE THERE YET?

Some teams claim that machine learning can predict autism with accuracies well beyond 95 percent, but those rates are unlikely to hold up under more rigorous test conditions, researchers say. Until the algorithms are that good, they are nowhere near

ready for clinical use—and they won't get that good without more experienced diagnosticians helping to guide their development: It takes clinical expertise to recognize and avoid the more obvious pitfalls in interpreting the available data.

“By and large, I think the biggest problem we have is people with data-mining expertise going to datasets they don't comprehend, because they're not being guided by a clinical perspective,” says Fred Shic, associate professor of pediatrics at the University of Washington in Seattle. “I think it's really important to work together when extracting deep truths; we need people with understanding of all sides to sit together and work on it.” Journal editors, too, should find reviewers with machine-learning expertise to look over related autism studies, he says.

Shic is co-investigator on a project that has developed a tablet-based app called the Yale Adaptive Multimedia Screener, which uses video narration to walk parents through questions about their child's behavior. “I think it has a lot of advantages,” he says, but adds, “I don't want to oversell it because honestly there are so many ways you can go wrong with these things.” To learn more, he said, researchers need larger studies with long-term follow up.

Shic says he makes a habit of scrutinizing the methods other researchers use and also checks to see if they replicate their algorithm's accuracy using an independent dataset. “Of course, we will see a lot of advances. We will also see a lot of snake oil,” he says. “So we've got to be vigilant and suspicious and critical like we've been about everything that comes up; just because it's couched in mathematics doesn't mean it's more real.”

Mathematics will never solve the ethical problems that may come with using machine learning

for autism diagnosis, others note. “I really don't think we should put the power of diagnosis, even early diagnosis, in the hands of machines that would then relay the results from the machine to the family,” says Helen Tager-Flusberg, director of the Center for Autism Research Excellence at Boston University. “This is very profound moment in the life of a family when they are told that their child has the potential to have a potentially devastating neurodevelopmental disorder.”

Styner points to the chance of false positives, or instances when a computer might wrongly identify a child as having autism, as a reason to move slowly. “I actually think something like Cognoa would be doing harm—significant harm—if it incorrectly predicts that the kid would have autism when [he or she] does not,” he says. “Unless you have a rock-solid prediction, I can't see how this is not something unethical to a certain degree because of those false positives.”

In Styner's own family, things turned out better than he might have predicted. His son Max, now 11, is academically gifted and benefits from a social-skills class and weekly play group. He is doing so well, in fact, that he may no longer meet the threshold for an autism diagnosis, Styner says.

Given his experience as a parent, though, he understands why families are so eager for earlier screening and diagnosis—and it still motivates him in his efforts to hone the potential of machine learning. “I can really empathize with families and their interest in knowing not just the diagnosis, but also what to expect with respect to severity of symptoms,” he says. “I certainly would have wanted to know.”

[This article was originally published in 2018.](#)

# THE PROBLEM OF OVEREXTRAPOLATION

BY JESSICA WRIGHT

*In the United States, the CDC's estimates of autism prevalence in Black children are based on just a few families.*

A survey that estimates autism prevalence in the United States includes too few Black families to yield accurate data, according to a 2019 study.

Researchers presented their analysis at the 2019 International Society for Autism Research annual meeting in Montreal.

The survey, called the National Survey of Children's Health, asks parents to respond to questions about the health of the children in their household.

The survey tends to report a higher prevalence of autism than estimates that rely on expert review of health records. The prevalence of autism based on the latter method is 1.69 percent for 2014, according to the Centers for Disease Control and Prevention.

The 2016 survey found that 2.5 percent of children in the U.S. had autism at the time of the survey. The survey also offered a breakdown by race: 2.79 percent in Black children and 2.57 percent in white children. The estimate for Black children is based on responses from just 80 families, however.

The number of Black families in the 2017 survey is even smaller.

For this survey, the researchers looked at the data for children who had ever had an autism diagnosis, not just those who had it at the time of the response. The survey reported a prevalence of 2.86 percent in white children and 2.63 in Black children. In this case, the figure for Black children is based on survey data from only 38 families with an autistic child.

"When you look at the numbers, 38 Black children with autism are supposed to represent our entire country," says Meredith Pecukonis, a graduate student in Helen Tager-Flusberg's lab at Boston University, who presented the findings. "This is ridiculous."

Black children with autism tend to be diagnosed later than white children and are often misdiagnosed with other conditions. They also have less access to services and tend to be underrepresented in most studies of autism.

In total, only 1,447 Black families filled out the 2017 survey, compared with 16,482 white families. Overall, 6.7 percent of families who responded to the survey are Black, whereas Black people make up 13.4 percent of the U.S. population, according to the 2018 census.

Black children are less likely than white children to be diagnosed with autism, and more likely than white children to be diagnosed with intellectual disability, developmental delay, behavioral problems, speech disorders or attention deficit hyperactivity disorder, according to the survey.

The findings suggest that some Black children with autism are misdiagnosed, Pecukonis says.

This article was originally published in 2019.

# IS AUTISM HARDER TO MEASURE IN SOME CULTURES THAN IN OTHERS?

BY CHLOE WILLIAMS

*Certain traits of autism seem to be culture-specific. That complicates work toward universal screening tools.*

Some autism traits look the same across cultures, and they could form the basis of a global screening tool, a 2019 study suggests<sup>1</sup>. Other traits, however, are specific to particular cultures, and this must be accounted for when designing autism screens and diagnostic tools.

Autism often goes undiagnosed in some countries, giving an artificially low estimate of prevalence. Most screening and diagnostic tests for the condition were developed in Europe and North America, and are based on Western cultural norms. But caregivers in non-Western settings may have different expectations of how children should behave, and children may be unfamiliar with cultural references in the tests.

In rural South Africa, for example, children are unaccustomed to singing “Happy Birthday” and blowing out candles on a cake—an activity they are asked to pretend to do when completing the Autism Diagnostic Observation Schedule. And a 2011 study suggests that Japanese parents often perceive a child’s disinterest in peers as shyness or modesty, valued traits in that culture rather than a red flag for autism<sup>2</sup>.

The 2019 study examines which items on the Autism Spectrum Quotient (AQ)—a 50-item questionnaire that caregivers complete—best distinguish children with autism in three countries from their typical peers. Overall, 28 items proved at least ‘acceptable’ for identifying autism in all of the countries, and 5 are ‘excellent,’ the researchers found.

“I was quite surprised how well the items worked,” says lead investigator Rosa Hoekstra, senior lecturer in psychology at Kings College London’s Institute of Psychi-

atry, Psychology and Neuroscience. “Hopefully, this can be one building block towards the bigger body of work exploring where culture sits in the puzzle of autism.”

The AQ is not commonly used as a clinical instrument. More typically, scientists use it to study autism traits in the general population, says Catherine Lord, distinguished professor in residence of psychiatry and education at the University of California, Los Angeles. Still, the research underscores the idea that nuances in wording influence how caregivers interpret the questionnaire and recognize autism.

“It’s a wake-up call,” Lord says. “We tend to forget that reading a questionnaire is a behavior.”

## CULTURAL CLUES:

The researchers recruited 154 children in India, 306 in Japan and 1,020 in the United Kingdom, all 4 to 9 years old. About half of the participants from each country have an autism diagnosis.

Caregivers completed the AQ in a language they are fluent in, rating their child on 50 common autism traits using a four-point scale: The two higher points indicate the presence of an autism trait. The researchers assigned each item a rating based on how well it differentiates between the two groups.

The number of items deemed ‘excellent’ at identifying autism vary by country: 16 for India, 15 for Japan and 28 for the U.K. But the researchers rate only five as ‘excellent’ across all three countries. These include questions that gauge a child’s ability to engage in chit-chat and to understand others’ intentions. Overall, 28 items are ‘acceptable’ or better for identifying autism in all three countries.

The researchers also found four items on the AQ that each identify autism in only one of the three countries. For instance, parents in the U.K. reported that their autistic child dislikes spontaneity more often than did parents in India or Japan. Another item evaluates whether a child often speaks in a monologue—a trait that flags autism only in Japan, the researchers found.

These insights highlight key cultural differences in autism traits, says Deborah Fein, professor of psychology at the University of Connecticut, who was not involved in the work.

#### GOING GLOBAL:

Cultural attitudes toward children may explain some of the results, Hoekstra says. Parenting styles in Japan and India may not allow for as much spontaneity as they do in the U.K., the researchers say. And it may be more socially acceptable for children to be chatty with adults in India and in the U.K. than in Japan, where children are expected to display quiet reverence toward elders.

There may also be issues in translating the test. For instance, in English, 'spontaneous' can mean 'I do things without planning' or 'I do things on my own initiative.' Translated versions of the questionnaire may skew toward the latter interpretation of the word, the researchers suggest.

The findings point to which traits researchers should include in universal screening tools, says Courtenay Norbury, professor of developmental language and communication disorders at University College London, who was not involved in the research. However, the participants with autism all have at least average intelligence and so are not representative of the entire spectrum, she cautions. Caregivers may also be especially attuned to

their children's autistic traits, as they already know the children have the condition.

"That's not the kind of context in which you're using a screening tool," she says.

Still highlighting culturally robust autism features enables researchers to compare studies from different countries.

"If you were using screening tools or diagnostic tools that included those [traits], then you could be reasonably confident that what we call autism in the U.K. bears some resemblance to what you call autism in India," Norbury says. The findings appeared in *Molecular Autism*.

Hoekstra is interviewing caregivers from different cultures within the U.K. to find out more about how they perceive autism and why traits differ across cultures.

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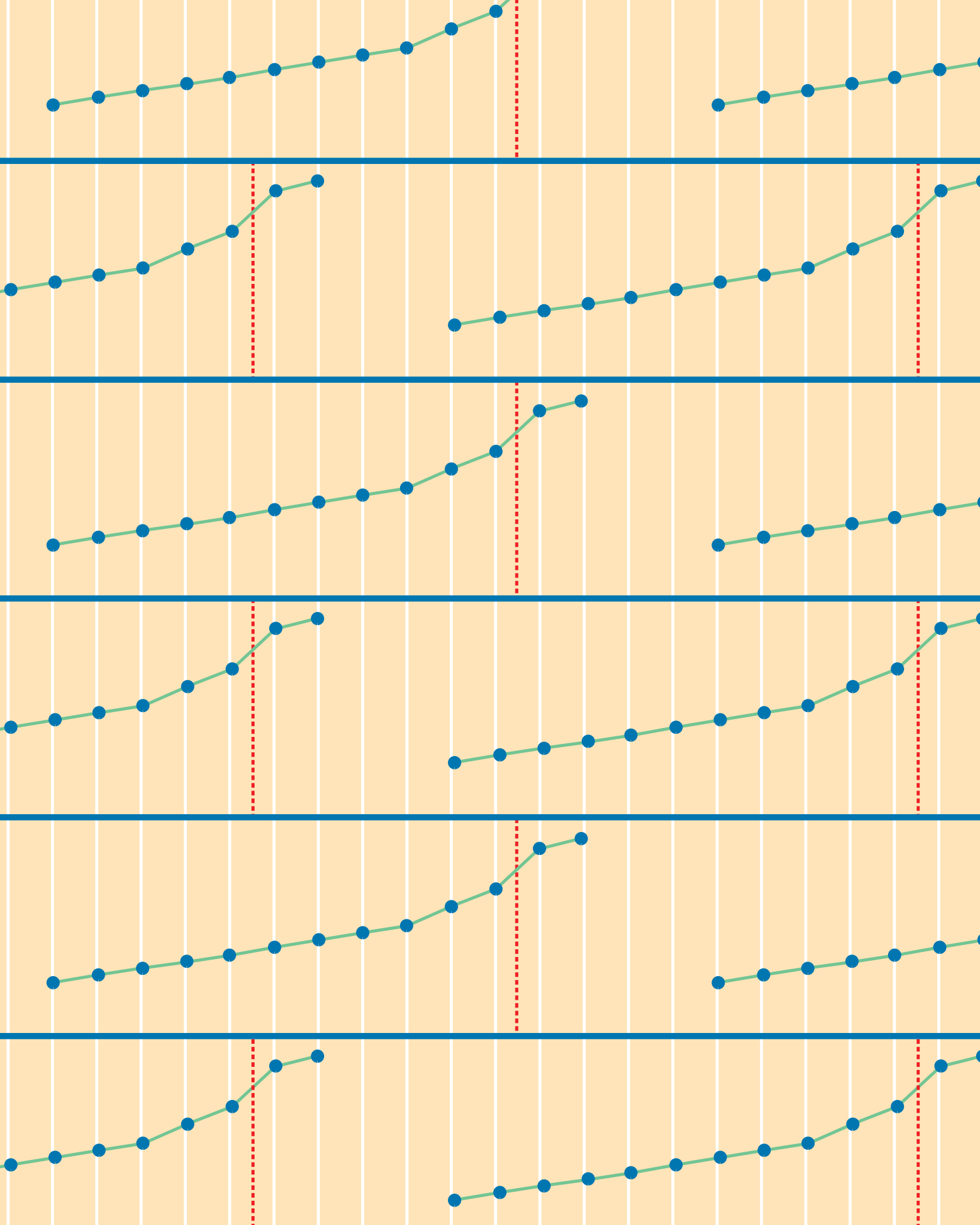
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