

Q&A

# Questions for Robert Joseph: How extreme prematurity ups autism risk

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Infants born prematurely have a **higher risk of autism** than infants delivered at term, and this **risk climbs the earlier a baby is born**. But it's unclear whether these autism features are merely a by-product of the complications of prematurity.

Autism in premature infants is no different from classic autism and not just a result of prematurity, says **Robert Joseph**, assistant professor of anatomy and neurobiology at Boston University. An early exit from the womb intensifies the biological factors that drive autism, putting preterm infants at heightened risk, he says.

In a 2009 study, Joseph's colleagues found that 21 percent of children **born before 28 weeks of gestation showed signs of autism** at age 2. In an extension of that work published in May, Joseph's team evaluated those same children at age 10<sup>1</sup>. About 15 percent of children born between 23 and 24 weeks of pregnancy have autism, compared with 3.4 percent of children born at 27 weeks, the study found.

We asked Joseph what he has learned about the link between prematurity and autism.

**Spectrum:** Several studies have tied premature birth to autism. What sets your findings apart?

**Joseph:** A large proportion of children in recent prospective studies had co-occurring sensory and motor impairments or extremely low intellectual ability. Those factors can make it hard to tell whether those children actually have autism or more global cognitive and neurological impairments often associated with extreme prematurity.

We examined a large cohort that's been followed prospectively from birth, excluding children with severe sensorimotor and cognitive problems. The children are now 10 years old, and we have their

entire histories: their demographics, their prenatal exposures, delivery characteristics, neonatal illnesses, and what they were like in their first month of life.

In the 10-year follow up, we found that autism is four times as common in children born before 28 weeks of gestation as in the general population. As others have shown, we found that the lower the gestational age, the higher the risk for autism. And we found that this is true regardless of whether the child has intellectual disability.

**S: What did you find most surprising?**

**J:** This is impressionistic, but what I found most striking was the lack of differences between the presentation of autism in children born extremely preterm and what I've seen in full-term children. We are looking at our data now to see if this impression holds up.

So many clinicians and other researchers have thought that preterm infants have an autism-like phenotype rather than “the real McCoy.” We've tended to exclude preterm children from autism research because we thought they had a different etiology. When we thought autism was largely genetically driven, we didn't want our study samples to have children who may have gotten autism in a different way. But I think we really see this much differently now.

**S: What is the new thinking?**

**J:** These children are born at a time when central nervous system development is still vulnerable. We know that these infants lack neuroprotective proteins that would be more abundant if they were born later. And we believe that in the absence of these neuroprotective factors, certain prenatal environmental exposures and events, and the inflammatory processes that accompany them, can lead to brain injury.

**S: A mother may go into preterm labor for many reasons. How might these reasons influence autism risk?**

**J:** We're trying to understand better how maternal and intrauterine characteristics and exposures put the child at greater risk for both preterm birth and autism.

We and other researchers are finding that one of the strongest predictors of autism in preterm infants is fetal growth restriction, being small for gestational age. It's possible that a lack of growth results in extremely premature birth, and the deleterious effects of exiting the womb midway through gestation further raises the risk of autism.

Preterm birth may cut short infants' exposure to factors that might protect against autism in a full-term infant. Not only are preemies entering the world early, but they may be exposed to maternal health problems that trigger preterm labor. These issues can be acute—for example, a vaginal

infection—or chronic, such as inflammation related to maternal obesity. Outside the uterus, they may also be exposed to environmental toxins such as tobacco smoke or toxic building materials; lack of money, food, and appropriate nutrition; and the psychosocial stress experienced especially by socially disadvantaged women.

**S: Most studies have found that autism is four times more prevalent in boys than in girls. But in your study, your team diagnosed two boys for every girl. How do you explain this difference?**

**J:** We're realizing that girls are **less likely to be diagnosed than boys** because their autism features look different from those in boys. Some of the girls in our study might have been missed if we hadn't evaluated them.

But the other possibility is that if girls are removed from the intrauterine environment too early, the hormones that normally **protect them from autism** might not be present.

**S: Where should we go from here?**

**J:** This is an excellent question. Most obviously, we need to continue education programs that, for example, encourage optimal nutrition or smoking cessation. For children who are born very preterm, health providers need to know that these children are at a substantially increased risk of autism.

Careful monitoring will lead to earlier identification at a time when interventions for autism are most effective. Monitoring may be especially important in socially disadvantaged communities, where affected children are **likely to be overlooked**. Some children born extremely preterm have excellent outcomes, but these outcomes may be even better with early intervention.

Biomedical research and clinical drug trials are underway to determine, for example, whether enhancing neuroprotection after preterm birth can reduce the damaging effects of inflammation on brain development. As we gain a better understanding of the neurophysiological processes at play, these kinds of intervention are likely to become increasingly important.

#### REFERENCES:

1. Joseph R. M. *et al.* *Autism Res.* Epub ahead of print (2016) [PubMed](#)