

NIEHS webcast transcript
Virtual Forum: Autism and the Environment
April 22, 2014

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Cindy Lawler:

Welcome and thank you for tuning in to our virtual forum on Autism and the Environment. This is a live webcast from the National Institute of Environmental Health Sciences or NIEHS, which is part of the National Institutes of Health. I'm Cindy Lawler, I manage an autism research portfolio here at NIEHS, and I'll be the moderator for today's event. We're glad you could join us for this very important conversation. Today we'll be discussing the impact of the environment on autism.

This virtual forum complements an ongoing series of community forums that we've been having for years. At some of our recent meetings, we've talked about safe seafood in Seattle, traffic pollution in Los Angeles, asthma in Boston, and the Gulf oil spill in New Orleans. With this virtual forum, we're extending the conversation to a national and even international audience on a topic of global significance.

Before we introduce our panel, I want to remind you that you can ask questions of our panel at any time. You can do this in two ways. You can use the question box on our webcast or you can also send us a tweet at our Twitter handle, @NIEHS. You can use the hashtag "AutismForum2014." We will try to get to as many questions as we can, but we may not get to everyone. In fact, we already have a number of questions that have been submitted, and while we appreciate that many people are seeking help for their family members with autism, this panel is not able to respond to any questions about specific symptoms or cases. We -- so please refer to health care professionals for those questions.

Here, what we can talk about is what research is showing regarding links between the environment and autism. We are very happy to note that we have a very -- a large number of registrations that have come in and we hope that everyone is logged in and is able to stay logged in for the hour. You should also know that the webcast is being recorded and will be made available on the NIEHS YouTube channel in the coming days.

So let's get started by having each of the panelists joining me today introduce themselves and we'll start with Heather Volk [spelled phonetically] on my right and we'll end with Linda Birnbaum who will make some brief remarks.

Heather Volk:

Thank you, Cindy. I'm Heather Volk from the University of Southern California and my research seeks to identify gene environment interactions for autism spectrum disorders.

Alan Brown:

Thank you. I'm Alan Brown from Columbia University and my research is on prenatal environmental risk factors for autism and a national birth cohort.

Irva Hertz-Pitticioto:

Thanks for having me, Cindy. I'm Irva Hertz-Pitticioto from the University of California Davis and my research focuses on the modifiable risk and protective factors and the mechanisms that they operate by and how we can intervene to reduce rates of autism.

Avi Reichenberg:

Hi, I'm Avi Reichenberg, I'm with the Ichan School of Medicine at Mount Sinai, New York, and my work focuses on both the genetic and the non-genetic causes of autism.

Linda Birnbaum:

And I'm Linda Birnbaum and I'm the director of the National Institute of Environmental Health Sciences and the National Toxicology Program. Our mission is to discover how the environment affects people in order to promote healthier lives.

So before we get to your questions, I'd like to give a quick overview of today's topics. The rates of autism spectrum disorder continue to rise in this country and we're really working hard to understand why. This research is important and urgent. Last month, we learned from the Centers for Disease Control and Prevention that one in 68 children are affected. We believe that many factors are behind this increase in rates. It can't just be genetics. Something in our environment may also be playing a role.

So NIEHS is funding research both here in the U.S. as well as internationally looking for links between autism and the environment. We know that pregnancy and the first few months of life are very sensitive periods of time when the environment can change how the brain develops. Scientists funded by NIEHS are looking carefully at a number of things that may alter the risk of a child developing autism, specifically environmental factors like industrial chemicals, heavy metals, flame retardants, air pollution, as well as infectious agents, nutrition, medical conditions, and complications during pregnancy.

These studies are beginning to provide us with some answers. We know that common exposures like air pollution can increase risk and taking prenatal vitamins early in pregnancy and consuming a diet with sufficient folic acid can help prevent autism. We've been supporting autism research here at NIEHS for many years. I expect we will continue to make progress and look forward to talking about it with you today.

Cindy Lawler:

Thank you, Linda. Autism is a complex and serious condition and it's affecting more and more people. I'd like to start the conversation with a few questions to get us up to speed on what we

know to date about autism. Heather, what is autism and is the definition of autism changing? Can you give us a quick reminder of what this disorder is?

Heather Volk:

Sure, Cindy. So autism is a neuro developmental disorder, probably first diagnosed in childhood and really characterized by deficits in social interaction, communication, and these children often have restricted to repetitive behaviors. What's really interesting now is rather than talking about separate classes of pervasive developmental disorders like autism or Asperger's syndrome, we're now going to be combining these diagnoses together talking about a broader class of autism spectrum disorder. It's really leading towards the study of this constructs on a broader scale thinking about severity of impairment as well.

Cindy Lawler:

Linda mentioned that the rates of autism have increased. Avi, can you give us a little more detail on the prevalence of autism? How many people are affected?

Avi Reichenberg:

So a most recent study suggested between 1 percent to 2 percent of every -- of all children have autism. The recent study that Dr. Birnbaum just mentioned suggested in the U.S. one of every 68 children is diagnosed with autism.

Cindy Lawler:

Alan, are there other disorders or conditions that tend to come together with autism and are there any connections between other neurodevelopmental disorders and autism?

Alan Brown:

Yes. It's been well-documented that children with autism have increased in risk of mental retardation and other intellectual disabilities as well as a high risk -- higher risk of epilepsy than the normal -- than the healthy population. In addition, some recent studies are suggesting that certain gastrointestinal abnormalities including inflammatory bowel disease are associated with autism as well as food allergies and hypersensitivity to certain stimuli. So it seems as if there's certain subgroups of autism that are characterized by the co-occurring conditions.

Cindy Lawler:

Irva, as someone who started looking for environmental risk factors for autism 13 or 14 years ago, as you look in those ensuing years, what is it that stands out to you about how research has evolved on understanding environmental risks for autism?

Irva Hertz-Pitticioto:

Well, we've started to make some progress. You know, 12, 13 years ago, I just started out in this field and, you know, looked around to see what we knew and it was pretty paltry, [laughs], in terms of how much research had been done. There were just a few clues. One had to do with congenital rubella -- children whose mothers had had rubella during the pregnancy. Another

clue was about thalidomide which was a medication used for a very short period of time because it was found to be too rather genic. But it did show us that, you know, we needed to cast a really wide net because one of those was a virus and the other one was a -- you know, a pharmacologic agent.

So in the last 13 years, I think we've identified a lot of clues now. Dr. Birnbaum told us a little bit about some of those. The nutritional factors -- we're -- we have data on periconceptual nutrition. You really have to start very early. There's the data on air pollution. There's been several studies now on pesticides -- some interesting literature beginning to come out. And you mentioned the issue of infections as well, so that's another area that needs to grow more, but it does suggest that there are -- there could be some role of either infection or inflammation. So -- and medications is another one where a number of studies have been pointing to certain medications that may interfere.

Cindy Lawler:

So leading up to this forum, we received a lot of questions and some of them were very similar. So what we've done is group -- bunch some of those questions together and I'll start with some of those. Linda, we received a few questions about funding. Can you give us a perspective on what the research investment is in this area?

Linda Birnbaum:

Well, the National Institutes of Health in FY -- the fiscal year 2013 spent about \$186 million on autism research. NIEHS, which is a relatively small institute at NIH, has spent over \$40 million in less than 10 years on research on environmental causes of autism, and in fact in FY13, we spent over \$7.5 million, which was a significant increase from what we spent, say, 10 years ago where we spent less than half that amount.

Cindy Lawler:

So another very common question we got was about vaccine research. Alan, I'll start with you. Can you catch us up on the latest regarding any connection between vaccination and autism?

Alan Brown:

Yes, and this has been a somewhat controversial area. However, there have been a number of very good epidemiologic studies. There was a lot of concern about the Measles, Mumps, and Rubella vaccine increasing risk of autism. There have been some very large studies that have essentially refuted that and have not shown any evidence of an increase in autism, and in fact, in a country like the U.K. where they got rid of the Measles, Mumps, and Rubella vaccine or decreased the use, the risk of autism continues to climb while the risk of measles, mumps, and rubella increased. There have been some concerns raised about other vaccines including total numbers of vaccinations given to people, but there has not been any clear link made as yet between those vaccines and autism risk.

Cindy Lawler:

Irva, what are your thoughts on that question?

Irva Hertz-Pitticioto:

Well, Alan just talked about sort of two of the vaccine-related issues that arise. One was the MMR and the other is this sort of increasing numbers of vaccines that we recommend for very young children at which -- the second one being a little difficult to actually study. The third issue that has been raised has to do with the preservative thimerosal in some of the vaccines and I think that literature is a little bit less convincing because it doesn't show any effect whatsoever but I find it not totally conclusive because of some flaws in those studies. So probably in the area where some further research might be helpful in, you know --

Linda Birnbaum:

Cindy, I'd like to comment --

Irva Hertz-Pitticioto:

-- settling --

Linda Birnbaum:

-- a moment if possible. I just think that we're beginning to understand that autism can be detected at very, very, very young ages long before even the first vaccination and certainly the multiple vaccinations occur. There have now been a number of studies that reported that as early as one to two months of age, children can be identified who will be somewhere on the autism spectrum disorder and obviously, at least in those cases, it pre-dates --

Irva Hertz-Pitticioto:

[affirmative]

Linda Birnbaum:

-- any exposure to vaccines.

Irva Hertz-Pitticioto:

Yeah. Yeah. I mean, not all cases are detectable at that young of an age, so there's -- I -- you know, I think there is some possibility for post-natal influences and vaccines would be one of, you know, dozens of things that we ought to be thinking about, but you're right. The -- for many children, probably very early insults are playing a role particularly in a pregnancy and early gestation.

Alan Brown:

And that isn't to say that the immune system isn't important or immune activation and we have evidence from our national cohort study that we may talk more about, but mothers with elevated immune -- a marker of immune activation -- their offspring have an increased risk of autism. So I don't think that means we need to rule out the idea that immunologic factors and immune -- and inflammatory mechanisms could play a role in autism.

Avi Reichenberg:

Just a --

Cindy Lawler:

Thank you --

Avi Reichenberg:

-- just one little thing, if I can, just to go back to the first thing said because I think a lot of the parents are concerned. Should I give my children the vaccine or not? What Irva actually said is that, you know, the evidence from epidemiological studies -- large epidemiological studies, large population studies carefully done are very convincing that there is no relationship between the MMR vaccine and risk for autism. So I think that's an important message if we could send from this forum to parents who are listening than this -- there is no evidence for a relationship between the MMR vaccine and autism.

Cindy Lawler:

Thank you. Let's move on. We have many, many questions to get to. We received a number of questions about multiple exposures. Linda, can you talk a little bit about the challenges researchers face when they're trying to identify not just one factor that may play a role but a combination of exposures that may be important?

Linda Birnbaum:

Well, I think air pollution is a very good example of a very complex mixture that has now been associated with autism in at least seven well-conducted epidemiology studies. I think that it is difficult to study mixtures, but mixtures are the reality of what we face. We live in a complex soup and while if we can understand if a specific exposure is associated with an outcome, we may be able to control that one exposure, but in most cases there are going to be multiple triggers that can play a role and we want to try to understand what those multiple ones can be.

Heather Volk:

And I think that's a very concise way to explain it. You know, if you think about air pollution as an exposure, that's, like, a mixture of multiple chemicals in multiple things there. And so trying to tease apart which one is important is very, very difficult. But you may be exposed to a certain amount of air pollution, but your mother may or may not have taken her prenatal vitamins and you may have pesticide use near your house or in your home. So there's a lot of factors that we have to learn how to handle those in our studies and how to put them together to have them really make sense and tell us a story.

Alan Brown:

And I think it's also important to recognize, as studies have shown and been mentioned, that taking folic acid supplements can decrease risk of autism and that when we consider an

individual pregnancy or an individual child, we need to look at both the risk and the protective factors together.

Cindy Lawler:

That's a good segue to the next set of questions. Heather, I'll have you start the ball on this. What kinds of advice can you give to a woman who's thinking about becoming pregnant or who is already pregnant and is concerned about some of the risk factor research that she sees in the news?

Heather Volk:

So my first advice to women usually being a young woman myself and having kids -- young kids is that, you know, to not make yourself too nervous. You see these papers and things get very sensationalized and it's very easy to get scared. Even myself -- working in this field, I feel very much that same way. You know, and it does seem to say to take your vitamins if you're thinking about getting pregnant. Just start taking prenatal vitamins early is what the research -- it seems to be playing out. But then once pregnant, you know, sort of good prenatal care is the best thing that you can do for yourself throughout your pregnancy. And that's one conclusive thing that we know can really make a difference and impact a child's health.

Irva Hertz-Pitticioto:

[affirmative] Yeah. Can I add --

Cindy Lawler:

Yes.

Irva Hertz-Pitticioto:

-- a few things to that? So if you're planning a pregnancy, there's now several studies suggesting that having an interval that's maybe about three years or longer between pregnancies is a good idea, that the very short -- you know, within a year or two years seems to be associated with a higher risk for autism. So that would be a -- one way to start. The prenatal vitamins and the studies show that by the time you're pregnant, there's not much protection from the point of view of --

Female Speaker:

[affirmative]

Irva Hertz-Pitticioto:

-- the autism. There are probably benefits to the child other than protection of autism, but to protect against autism -- it's actually the few months just before and the very first month of pregnancy that seem to be the most important. And then, you know, other things -- just being healthy, avoiding, you know -- if you have to apply pesticides, look for, you know, the non-toxic kinds of alternatives, staying away from, you know, heavy pollution, cigarette smoke, those sorts of things. And then a little bit of literature suggesting that, you know, controlling weight -- that

obesity at the time of -- pre-pregnancy obesity can -- seems like it may also be a factor that could increase risk in the child.

Alan Brown:

And we don't have strong evidence for this yet, but because inflammation has been associated --

Female Speaker:

Yeah.

Alan Brown:

-- the avoidance of certain infections, at least staying away from individuals with clear, obvious, severe infection like influenza or severe bacterial infections maybe a good idea not only in preventing autism, but of course other neurodevelopmental disorders.

Avi Reichenberg:

If I can just mention one thing -- is that we've heard of -- from my colleagues on the panel of a number of behaviors or health behaviors that could maybe help, but they would help any pregnancy.

Female Speaker:

Right.

Avi Reichenberg:

There is in fact -- we don't yet have a prescription that would prevent autism in any child or any other developmental disorder and we need to be very careful by not telling people that they need to do certain things and that would definitely, you know, reduce the risk for autism. We don't know. These are statistical associations, they're relevant to a wide range of developmental outcomes, and they're relevant in general for a better outcome of a pregnancy. Healthy living, visiting your health providers, following health guidance, eating in a healthy way all help -- taking your food supplements. They would help in general to increase the chances of the pregnancy -- would be successful and the outcome of the children would be a good one. So we don't yet have a prescription that would reduce risk for autism unfortunately.

Cindy Lawler:

So here's a specific question we got from Valley Spring [spelled phonetically], New York and it's a simple question. I'm going to give it to Avi and the rest of you can join in. Simple question. I think it'll be a complicated answer. Is autism hereditary?

Avi Reichenberg:

The simple answer to that is yes and the more complex answer to that is not always and it will be a very long lecture for me to give on why exactly it's not always. But there are certain causes of autism that are not inherited in the sense that you -- you know, they might be genetic, but you don't get them from your parents, so that's non-inherited causes of autism.

A lot of autism might be inherited, but not in a simple way. It might defer between different people and in many cases there will be also environmental factors at play or all in something called gene environment interactions, which we are only beginning to understand and will take a long time to clear up both the genetic part, heritable part, and the non-genetic environmental part and how they interact. So the simple answer yes. The longer, complex answer, is no and that's it I think, [laughs].

Linda Birnbaum:

I think it's important actually to say that most cases of autism -- we don't know what -- you know, what the --

Avi Reichenberg:

Causes.

Linda Birnbaum:

-- what the causes are and we do know that if in a family there's one child with autism, there's an increased risk that subsequent children will have autism, and people have said, "Well, that clearly means a genetic component." And I would ask the question -- most children growing up in the same household have similar environmental exposures as well. So it's -- again, it's probably as you suggested Avi -- maybe an interaction between genes and the environment. There are a couple of unusual syndromes where the child will have autism and those are clearly largely genetic driven, but from the studies looking at identical twins, it's clear that it's not just your genes, but your environment is playing a role as well.

Alan Brown:

Yeah, I mean, if it were --

Irva Hertz-Pitticioto:

Well, and act like --

Alan Brown:

Sorry.

[laughter]

Cindy Lawler:

Irva and then Alan.

Irva Hertz-Pitticioto:

Yeah, I'd like to add that -- you know, it's not an either or and that there -- you know, in most cases, there's multiple factors, probably multiple genes, and multiple environmental factors operating maybe at different time points, you know, starting before conception and all the way

through various stages of prenatal development where the brain is forming in its very early stages and the neurons are figuring out how to connect to each other and form what we call synapses. So it's really complex --

Female Speaker:
[affirmative]

Irva Hertz-Pitticioto:

-- but I think in most cases you can't pin it on one factor and I think that's something that, you know, families need to understand -- that it -- you know, it's not, oh, that one thing you did at one point or something that happened to you. You know, it's complicated.

Cindy Lawler:

Heather, I'm thinking of your work on air pollution and genetic susceptibility as a nice example of how you have to have both. Do you want to talk a little bit about that?

Heather Volk:

Sure. So in some of our research, we've actually looked at a gene that has been associated with autism, and I should say that it's been associated with autism, meaning there are versions -- a variant of this gene that is often more frequent in children and cases with autism are transmitted from parents to children, but it's not diagnostic. It's not anywhere close to being diagnostic in and of itself. And we've looked at that in conjunction with air pollution exposure and found that kids who are exposed to higher levels of pollution, either from traffic or regionally in their area, with the risk version of this gene had a much amplified or increased risk of autism compared to - relative to not having the gene and not being exposed. And that's one very simple early example that I think we're finding now.

I -- it's taken us a long time and Irva, you mentioned at the beginning of this webcast that, you know, you started in the field when we didn't know much at all and it's wonderful to be able to sit here and have a few things that we do think we know now and understanding how genes and the environment work together is I think one of the important next steps that hopefully we'll take. But it is difficult to do properly and I think unfortunately sometimes that's why, you know, science is slow which I understand can be frustrating to parents who want an answer and want to know what one thing you can do to make a difference.

Alan Brown:

Yes, and following on that, I mean, if autism was purely genetic, one would expect that if a twin had autism and their co-twin, their identical twin, would also have autism. That isn't the case and as in your work, you do find that some people who are exposed to high levels of air pollution. Most of their offspring do not get autism as well as those who have the gene.

Heather Volk:
Right.

Alan Brown:

Most of them do not, and even among those in -- and you'd have to tell us what the data show, but even among those who have both the gene and the environmental exposure, many if not most probably do not get autism.

Heather Volk:

That's --

Alan Brown:

So we're talking about a -- what we call a multi-factorial disorder, one with many, many causes.

Heather Volk:

That's exactly right, Alan. I mean, even now when we're looking at two factors together, it's not perfectly predictive. We don't have a good way or Avi mentioned we don't have a prescription or a diagnostic test.

Irva Hertz-Pitticioto:

Yeah. Well, and the genetics gets complicated because in our -- so you saw the gene environment interaction with air pollution. We saw also similar kind of a gene in susceptibility - - certain susceptibility genes increased the benefit that you might have from taking those prenatal supplements and interestingly, there were genes in the mother and genes in the child that made a difference. So, you know, it's -- it gets, you know, complex --

[laughter]

-- thing that keeps coming out here. And our -- I just wanted to touch on what you mentioned about -- you know, even if it runs in families, it could -- that could be because there's the same environmental factor. You know, siblings usually have the same intrauterine -- it's not exactly the same time point, but it's the same uterus and the same mom who, you know, has certain things about her that carry from one pregnancy to the next. So that, you know, continuity can also have something to do with family recurrence rates --

Heather Volk:

Yeah, we've --

Irva Hertz-Pitticioto:

-- for autism.

Heather Volk:

-- recently started trying to look at environmental exposures in families with multiple children with autism, and so hopefully that's something that we'll have some more information on soon.

Cindy Lawler:

Avi, what do we know about birth complications in autism and any thoughts on how changes we've seen in how women receive their prenatal care or labor and deliver practices over the past 20 years or so may be impacting the rates that we see?

Avi Reichenberg:

So that's a big question.

Cindy Lawler:

I'll have you start it and then --

Avi Reichenberg:

Okay, I was --

Female Speaker:

[laughs]

Avi Reichenberg:

-- hoping for some help from my colleagues on the panel. I think the first thing as an epidemiologist that you would look for is complications in pregnancy or during delivery and their relationship to autism. It's been looked at in multiple psychiatric and neurological disorders and this is a first, I think, necessary step that we should take. And one other reason to look at that is that medicine gets better, especially perinatal, neonatal treatment, and the treatments that children who are born with complications or after a difficult pregnancy we are receiving now are different than what they received 20 years ago and those children actually develop better.

So one of the -- the two I think main factors that have been looked at were pre-term birth, being born too early, and low birth weight. Now, they kind of go together because a pre-term baby would also have low birth weight and in many -- 20, 30 years ago it was almost always that the child that was born early would be having also a low birth weight. But I have to say that even the evidence that we see there is still not conclusive. So there are some studies that are showing that pre-term birth is associated with risk for autism. Other studies are showing that there is no association. There is research on smaller samples of very pre-term babies, and these are relatively small studies. So some of us here are doing studies of thousands and hundreds of thousands and millions.

We don't even [unintelligible] studies that are following up -- a couple of hundreds, maybe 800 children, and they have been suggesting that very pre-term birth, birth before the age of 26 weeks of gestation, is associated with a high risk for autism. Now, this needs to be followed up and some of the colleagues here are trying to follow up on that. It takes time to figure this out, but these children are not necessarily at higher risk just for autism. Those studies -- at the same that they're saying there's a higher risk for autism, there is also a higher risk when the child is born

so early on for other adverse outcomes and not necessarily just autism. So there is a second question which is all these complications which have been linked to other psychiatric neurological conditions -- are they specific to autism or is it something more general?

Irva Hertz-Pitticioto:

And that's not just true for the complications. I mean, this is -- you know, with the prenatal vitamin supplements, we saw benefit also for developmental -- other kinds of developmental disorders and I can't remember -- if you'd looked at that and then the air pollution --

Heather Volk:

Yeah, I mean, there is --

Irva Hertz-Pitticioto:

-- it's a common theme [spelled phonetically].

Heather Volk:

-- a prod-letter [spelled phonetically] chart that's sort of growing now looking at associations with air pollution exposure with autism but also broader neurodevelopmental effects, decreases in I.Q., poor cognitive functioning kids as they grow older. So a lot of these factors as you were really nicely explaining seem to be pretty cross-cutting -- cutting across neurodevelopment and, you know, I think the question for us to figure out is what makes it specific to autism.

Alan Brown:

Yeah, and following on some of your points, Avi, specifically, the very pre-term especially have very high rates of fetal hypoxia and later events, later complications, abnormalities in the brain that could mediate that -- those effects that are seen. So for example, children who go on to develop autism have much higher rates of fetal hypoxia, low Apgar scores, more time spent in the neonatal intensive care unit. So I think all of these risk factors are operating together. The low birth weight is an interesting one not only because it's explained by preterm birth, but also by slower growth while the baby is in the womb, and for that we don't have complete explanations as to why, but there could be various prenatal factors that may slow birth weight, slow the fetal growth.

Linda Birnbaum:

But kind of just like we were saying before when we were talking about a healthy pregnancy, you can't worry about everything and there are many, many babies who are born early or born with low birth weight who turn out to develop perfectly normally.

Avi Reichenberg:

Yes.

Female Speaker:

Yeah.

Avi Reichenberg:
That's true.

Alan Brown:
And that there have been many improvements as Avi has made in prenatal care which have helped to I think decrease a lot of that morbidity. It's also led for some children to survive and these are children who often have certain birth defects or intellectual problems. Another big issue I think is that while the science of obstetric complications is moving forward, it's not moving forward as quickly as it was. However, a big question, a big issue, is the delivery of good obstetric care, and I think that's a health services delivery issue which is I think also -- should be recognized.

Cindy Lawler:
So this is a specific question that came in a few minutes ago from Fort Belvoir, Virginia and I think we've already seen in some of the research areas that are being discussed so far that, you know, the body of work is not yet definitive. There are -- sometimes are conflicting data. So the question is how can the public know which research studies to believe? I mean, we all, you know, see the headlines, but as a member of the public or as a parent, what's the strategy for trying to sort of understand --

Linda Birnbaum:
So --

Cindy Lawler:
-- what are often conflicting --

Linda Birnbaum:
-- stab at that. I think when a new study comes out and it gets a lot of hype, one of the things you want to try to read is is this a repetition of something that someone else saw? Is this related to things that make -- you know, that make sense? Sometimes things get a lot of play and they don't make sense, but I think that the strength of science is in the repetition when in fact you find similar studies coming up with a similar result.

So, as I mentioned, air pollution and its association with autism spectrum disorders before, we now have at least seven studies -- well-conducted studies in different populations and some of them are even using different kinds of air pollution or different mixtures of the complexity that we deal with with air pollution, and they're all showing this association. So that gives confidence that this may be a real agent involved in the increasing prevalence of autism spectrum disorder.

Cindy Lawler:
Heather, do you want to add to that?

Heather Volk:

Yeah, I think what -- Linda's point about replication and repetition of the results is really true and we were seeing that in air pollution literature, we're seeing that in the maternal [spelled phonetically] folate supplements and prenatal vitamin data, you know, and we're seeing that even with other risk factors -- things like advanced maternal or paternal age. And so those are -- that once you start to see that in the science -- sort of different scientists from different groups attacking the same question in different ways with different tools, and if we end up at the same point or similar point, it does start to let you think that this might be real. This might be something that's worth understanding better and trying to learn about the mechanism and then thinking about how we can intervene, how we can advise people.

Cindy Lawler:

So I think with air pollution there have been a -- several studies now that do seem to point to an increased risk. Here's a specific question that came in earlier from Boulder, Colorado and the question is the -- in general, we think of the air quality as improving in the United States over the past few decades while the rates of autism clearly are rising and then you think about China. Oftentimes a country with fairly serious levels of air pollution, but the autism rate is lower. So can you talk us through how to sort of explain that --

Heather Volk:

Well, sure --

Cindy Lawler:

-- type of --

Male Speaker:

[affirmative]

Heather Volk:

There's several aspects tied up in that question I think. So, you know, one really I think is that they -- the air pollution studies that have [spelled phonetically] been published haven't been trying to really explain the new cases that are occurring, right? We've been looking at associations and current recurring cases. And so we can look for environmental factors that sort of help explain rates that are current, rates that have always been there because overall saying it's likely not all one factor. So I think that's important to think about and are -- do you need to have a specific genetic background as we talked about earlier and be exposed to pollution to then have that increased risk? So that's sort of two ways to think about it.

And then the last way is that the pollutant mix keeps changing. So overall, what we measure and what we monitor has gotten better across the U.S., but there are particles smaller than the ones we monitor now that are not routinely monitored and its -- animal [spelled phonetically] studies

show us that those really can affect the brain and possibly affect the placenta developing. So there's -- there isn't necessarily a fact that, you know, because pollution and air quality overall --

Female Speaker:
[affirmative]

Heather Volk:
-- is getting better and autism is going up, that it doesn't make sense. It's -- the question is a little more nuanced than that unfortunately. It's understanding what we're exposed to now and how that has changed over time as well.

Irva Hertz-Pitticioto:
Yeah. Well, I think there's also -- maybe it's -- I think people have a rosier impression about time trends in air pollution because certainly our legislation dating back to the '70s -- we began to see air pollutant -- air pollution levels definitely going down, but the number of vehicles on the road has been going up so rapidly and, you know, people bought -- driving bigger cars that pollute more. So, you know, I don't think it's totally clear that gee, you know, in this last 10, 15 years where the autism rates have been really -- at least the number of diagnosed cases has been going up steeply that that necessarily -- that there's not some increase going on with air pollution.

But I think there's a more general question or issue here, which is do -- should we be looking only for exposures that are rising while the autism rates are rising? And, you know, the causes of the rise in autism and the causes of autism are overlapping but they're not the same. They're not the same because we know part of the rise is better diagnosis, more complete ascertainment, kids are being identified as having autism and not being misclassified let's say with other kinds of diagnoses. So part of that rise is just -- we're counting better. And so in that case, you have to explain the backgrounds including some of the missed cases of the past --

Female Speaker:
[affirmative]

Irva Hertz-Pitticioto:
-- and the causes of that as well as the causes of the rise and --

Male Speaker:
[affirmative]

Irva Hertz-Pitticioto:
-- that's -- it's -- I think it's a misconception that people think anything that's not going up can't be a cause of autism and there's so many factors. So you can also have a situation where, yes, it could be going down but it could have been a cause and it could be because of interactions with other things that are going up that would make it --

Alan Brown:
Yeah, I think that --

Irva Hertz-Pitticioto:
-- a causal factor.

Alan Brown:
Sorry. I think that underscores an important point which is that drawing inferences between individual level risk factors and what goes on in an entire population are very different things. I was asked -- I've been doing a lot of studies on toxoplasmosis. It turns out in certain countries, the rates of toxoplasmosis are very high because people leave their cats outdoors and they acquire it more and we have found it associated with schizophrenia. And people would say, "Well, then why isn't the rate of schizophrenia really high in that population?" Well, it's because the likelihood of getting schizophrenia from toxoplasmosis is not very large and as you were alluding to, there are many, many other risk factors that may be operating -- be operating to protect against that outcome in that population. So it's really an individual level versus population level question I think that this is --

Linda Birnbaum:
The other --

Alan Brown:
-- addressing.

Linda Birnbaum:
-- thing I want to mention is you asked the question about -- well, what about Beijing or Delhi or some of the other places where we know that the air pollution is horrendous? And the answer is we don't really have good data on what the prevalence of autism is in those populations. It's really an undiagnosed issue in many of those populations. I think that some of the data that's come out of South Korea suggesting that the prevalence of autism in their population is about I think one in 37 and I think many people in the autism field -- that's where we're heading once we do a better job at fully diagnosing and ascertaining the cases.

Alan Brown:
And I think it also has a lot to do with how you ascertain cases because in that South Korean study, autism was diagnosed differently than it's been in certain other studies.

Cindy Lawler:
Avi, get us started on -- I've heard a lot about how the age of the mom and the dad might affect risk for autism. What do we know now?

Avi Reichenberg:

Well, I think this is one risk factor that received a lot of attention -- this age of dads and age of moms at the time of conception or the time of birth of the child in part because it's intriguing and in part because technically it's easier to measure and it's measured very reliably. We know what the age of the dad is, we know what the age of the mom is, and we can look at how they're related to the outcome of autism in the child.

There is a huge number of studies and meta-analysis, which is a way of putting data together and giving kind of a summary of different studies, that show that older age of dads is associated with an increased risk for autism in the child. The same evidence also comes out for maternal age, so older age of mom is also associated with increased risk for autism in the child. There are certain questions that still remain unanswered. So we know something about some of the mechanism that's been linked to older age of dads -- being said to be something called de novo mutations, or mutations that appear in the child but are not present in the parents and perhaps something called epigenetic changes, which is occasionally the effect of the environment on the genetic material and how it changes.

But we don't -- this is not the full story probably. There might be more complicated other or different mechanisms that are related. We don't yet know if paternal age is the same or works independently of maternal age. Do they operate in some sort of an interaction, some synergy that happens between them or is there something else that we have missed or didn't look at properly that is available?

It is, however, a very interesting topic. My group is looking at it together with other large international collaborations. I know that other groups, including those sitting here right next to me, in the U.S. have been looking at it over the past few years and Alan has been doing work in Finland. And it is a field that brings together both molecular geneticists and epidemiologists. It doesn't happen always. It's sometimes very difficult to do. But both geneticists are looking at the molecular level and people who study animals are looking at animal models where you can control for different factors more carefully and epidemiologists like us look at population-based relationships trying to find out if there is a -- some certain age where the risk is highest or is it something that develops gradually and will tell us something more about the causes of autism.

Irva Hertz-Pitticioto:

But the -- it is both maternal and paternal. I mean, the -- some studies seem to show a little bit more in fathers, some more in mothers, but really, the -- you know, the studies as a whole seem to suggest that both of those play a role fundamentally. And then age is also -- you can think of it -- well, it's a risk factor. It's something kind of intrinsic. But age can also be a proxy for, you know, accumulated toxins. It can be a proxy for greater risk of autoimmune conditions, even talking about inflammation. So it's -- you know, it's actually a complicated variable of its --

Avi Reichenberg:

Yes.

Irva Hertz-Pitticioto:
-- in and of itself.

Avi Reichenberg:
It's very compact and interesting and straightforward to talk about de novo mutations even though -- even the mechanism of de novo mutation is not straightforward and simple.

Irva Hertz-Pitticioto:
Yeah.

Avi Reichenberg:
But clearly, there -- older age of dads and moms can harbor many, many other different factors. But what -- you know, I think we both agree that while a lot of OBGYN specialists ask the mom, "What is your age?" and then there is this risk table of what could happen and they follow very carefully -- all the moms. Maybe they should ask what was the age of the dad and --

Irva Hertz-Pitticioto:
[affirmative]

Avi Reichenberg:
-- carefully monitor that pregnancy as well.

Irva Hertz-Pitticioto:
Yeah.

Alan Brown:
And I think --

Irva Hertz-Pitticioto:
I'll buy [spelled phonetically] that.

Alan Brown:
And I think this gets back to an important question that you raised earlier, Cindy, which is how can scientists and the public have more confidence --

Female Speaker:
[affirmative]

Alan Brown:
-- in the findings that are coming out and Avi has alluded to something that actually a lot of us are interested in -- a lot of other scientists in the field, which is bringing together what we're seeing in epidemiology with animal models where there are biologically plausible mechanisms. And those mechanisms are very complex as you mentioned, but that may be a way, by bringing

it together with the epidemiology and other clinical work, at arriving at a more coherent answer as to our confidence that these are true risk factors for autism or for other developmental disorders.

Avi Reichenberg:

I think that the evidence coming from the paternal and maternal age is a very good example of how information is aggregated into a coherent story, into mechanisms, into, you know, the understanding of how disorders develop.

Cindy Lawler:

We've got a couple of questions that have come in related to the big sex difference in rates of autism. So could the panel comment on what the implications of this might be for environmental factors and how they might interact with any sex-specific responses?

Linda Birnbaum:

I'll start and then let the people who may know -- will know more than I do, but there are many, many different kinds of health conditions which are much more common in one sex than another. Autism happens to be about four and a half times more common in boys than in girls. Autoimmune conditions, which may play a role in autism, are actually much more common in women than in men. So is there some kind of protective role that the immune system might be playing in women or do we have to have more insults in order to cause autism in a female child than we do in a male because there's maybe a more protective immune system to begin with? I mean, I think there are many, many questions and many disease and I think that we should use the sex difference and try to understand that and maybe especially using our animal models to help to understand that, to shed light on explaining the situation in the human population.

Cindy Lawler:

This is one for Irva from Apopka, Florida. What is the connection, if anything, between pesticide exposure in autism and have there been any studies on the rate of autism among farm workers and rural agricultural communities?

Irva Hertz-Pitticioto:

Right. Well, there have been several studies looking at pesticides. One -- you know, several have been done in California in the central valley which is a heavy agricultural region and farm worker -- one study was actually done in a farm worker community called the Chimako [spelled phonetically] study and then others have been done in other places. So -- but of course, pesticides are actually a pretty broad group of compounds and different chemical structures if you're looking at what are called the organochlorines or the organophosphates or the pyrethroids. And some studies are looking at one and some are looking at another. There are three studies now that have -- that seem to suggest organophosphates might have a relationship with autism and it's interesting because organophosphates have also been linked to cognitive impairments. And in fact, I believe that was part of why they've now been banned for household products and they're still used in agriculture --

Linda Birnbaum:

Some of them were removed from the market. They were regulated out in 2002 --

Irva Hertz-Pitticioto:

Yeah.

Linda Birnbaum:

-- in part because of cognitive but also other reasons. But although they're no longer used in household products in this country, they certainly are used in agricultural exposures in this country. So if you happen to live or work near farms, you're likely to have exposure to those.

Irva Hertz-Pitticioto:

And the interesting thing about exposure is that studies doing -- taking biological specimens, blood specimens or urine, and looking at metabolites of those compounds are finding -- I mean, I think the theory was that levels would go down but it looks like it's not going down as much as we thought and that the measurements of organophosphates are still pretty high in just ordinary populations that have been looked at. So it is a concern. It is a concern.

Linda Birnbaum:

Cindy, I just want to make a comment which is I think that that's a -- really an excellent question that we just got and I'm thinking of we have a study we've been doing for 20 years following farm workers and their spouses and tending to look at their health effects in both the men and the women and we have very specific pesticide use information -- all these. And it's -- we've been looking at a lot of health end points [spelled phonetically] in adults, but I wonder if it would be possible for us to ask questions about their children's health and that might be a place because there are over 50,000 farm works and 31,000 spouses involved -- might be a really rich source of data that could be explored. So thank whoever asked the --

Avi Reichenberg:

[laughs]

Linda Birnbaum:

-- question. Thank you.

Irva Hertz-Pitticioto:

Yeah. The good old agricultural health study.

Linda Birnbaum:

[laughs] Right?

Irva Hertz-Pitticioto:

Yeah. Yep.

Cindy Lawler:

So we have a few questions about the topic of regression. So we have some kids that seem to develop normally and then they regress, so this is a question about is that a special group and do you think that -- you know, the risk factors for that particular group may differ from, you know, other children with autism? You know, I've often heard that, you know, if it's not one autism, it's many autisms. So can somebody talk about that group of children who seem to develop normally and then the -- regress? Do we know -- what do we know about their risks?

Irva Hertz-Pitticioto:

Well, there definitely is a subset of children who seem to be developing -- pretty much hitting the milestones on target and then at a certain point they really begin to lose functionality, lose language, lose social skills, stop making eye contact. I would say we don't know very much about that subgroup. Our research team tried to start looking at the regressed group and the -- what we call the early onset group, but then there was a study that came out that actually said that -- that found that, [laughs], that just asking parents, "Did your child regress?" turned out not to be as accurate as, you know, if you had actually -- had been taking -- looking at the children longitudinally over time -- that there were big discrepancies between what parents had noticed or not noticed and what the clinicians had seen when they were looking for it.

So it turned out we ended up feeling like the data that we had was not good enough to look at that question, but it is a question. Are there subsets of children with autism? That's one example -- regression and not [unintelligible]. You talked about a lot of different co-occurring conditions. Might there be different environmental factors in children who for instance have these strong gastrointestinal problems or the children who have, you know, autoimmune kinds of conditions? So it's --

Heather Volk:

And I think we're --

Irva Hertz-Pitticioto:

-- wide open, [laughs].

Heather Volk:

And I think we're in a fortunate place now where they -- there are several longitudinal studies of moms who have had a child with autism who are enrolled in research studies when they're pregnant with their next baby -- are now being followed longitudinally in those -- that subsequent baby is being evaluated over time. So hopefully those studies will help us answer questions about things like regression and when it occurs and what potential triggers there might be and those are underway now.

Alan Brown:

And it also seems to me that in talking with many clinicians in autism that it's often hard to

define what is regressive autism. Is there a clear definition of it that we can use in our research studies? I believe there is, but I think more work needs to be done in the definition.

Cindy Lawler:

So here's one from our website that came in from Tempe. I'll let you start off on it, Heather. How can families reduce air pollution in their house such as with a HEPA filter and how does someone find out what they have been exposed to?

Heather Volk:

So that's really a big, loaded question.

Female Speaker:

[affirmative]

Heather Volk:

I mean, I [laughs] think that, you know, regarding filters, we hope that they're working. I think that we need to do some good studies to know that for sure that they're working the way they're supposed to. You know, I live in Los Angeles and there's a lot of schools that have put them in because they're located near freeways or busy roads or manufacturers. And we need to know for sure I think that those things are working. So unfortunately I can't tell you -- so I couldn't tell someone specifically "Go buy this filter for your house" quite yet.

You know, in terms of limiting exposure in your home and what you can do, there are guidelines in place for people with respiratory diseases for example and vulnerable populations to -- who are vulnerable to air pollutants and sort of guidelines saying, you know, to limit your vigorous outdoor activity on very poor air quality days and things like that. So if you live in a highly polluted area, those sorts of guidelines that are in place and are established are things I think that are really worth it to consider.

But, you know, broadly pollution as the idea of what you can do to intervene is a very good one, you know, to think about where -- what you're exposed to and what you can do. I mean, Irva mentioned earlier perhaps you might think about trying to use non-toxic products if you can. You know, it's those sorts of things that can potentially really help make a difference.

Linda Birnbaum:

But we do know that the most effective actions that make a difference are the things that are done for public health that are done --

Heather Volk:

Yes.

Linda Birnbaum:

-- generally are much better than telling people they have to change their behaviors.

Irva Hertz-Pitticioto:

Yeah.

Heather Volk:

Yeah, that's very true.

Irva Hertz-Pitticioto:

Yeah. So, I mean, really that it comes down to these more regulatory standards being set, developing more alternative fuels that, you know, produce less pollution, different, you know, vehicle, you know, energy -- help me here.

[laughter]

I'm losing my language.

Avi Reichenberg:

New CO2 emission --

Irva Hertz-Pitticioto:

Hybrid cars --

Avi Reichenberg:

Yes.

Irva Hertz-Pitticioto:

-- and the electric cars would make a big difference in --

Linda Birnbaum:

Well, they would --

Irva Hertz-Pitticioto:

-- air pollution.

Linda Birnbaum:

-- lower some certain kinds of air pollutants. They would not necessarily impact other kinds of --

Irva Hertz-Pitticioto:

Other things that --

Linda Birnbaum:

-- pollutants and we do know that people spend most of their times indoors now and overall we haven't paid very much attention to the indoor environment other than when we're talking about

indoor cook stoves in less developed countries where we have people who are being impacted there with respiratory illness and so on.

Cindy Lawler:

So Alan, we've received several questions about the risk of ultrasounds during pregnancy. Are there any risks?

Alan Brown:

I would say that the -- it's a possibility but that has not been well investigated. There's some evidence that there may be some slight increase in temperature as a result of ultrasound and during pregnancy because it's a vulnerable period. We can't simply discount it, but I would say that many more studies need to be done. Those are very difficult studies to do however because ultrasound is so common. It's almost universal in certain countries.

One suggestion made is that one can look at different frequencies emitted and energies emitted by different ultrasounds and see if there's any correlation between that and autism risk, but those would be very difficult studies to do. That has gained a lot of traction in the population because of some people who are passionate about it and I wouldn't say it shouldn't be studied, but there really is no clear evidence. And I -- my current view is that ultrasound still does far more good than it does harm.

Cindy Lawler:

Unfortunately we've run out of time for today's forum on Autism and the Environment. I want to thank our panel of experts: Heather Volk from the Keck School of Medicine and Saban Research Institute Children's Hospital Los Angeles; Alan Brown from Columbia University; Irva Hertz-Pitticioto from the UC Davis MIND Institute; Avi Reichenberg from the Ichan School of Medicine at Mount Sinai and Seaver Center for Autism Research and Treatment; and Linda Birnbaum, the director here at the National Institute of Environmental Health Sciences. I'm Cindy Lawler from the Division of Extramural Research and Training. I want to thank you very much for joining us today. We couldn't get to all of your questions but we hope you got some useful information in our one hour virtual forum. For more details on autism and the environment, please visit our website at www.niehs.nih.gov. Thank you.

[music playing]

[end of transcript]