

# Autism Research Review

I N T E R N A T I O N A L

A quarterly publication of the Autism Research Institute—www.Autism.com

Reviewing biomedical and educational research in the field of autism and related disorders

## High blood glucose levels in pregnant women may increase risk of autism

Children of mothers who have elevated blood glucose levels during early pregnancy may have significantly increased odds of developing an autism spectrum disorder (ASD), according to a new study.

Anny Xiang and colleagues analyzed electronic medical records data from more than 35,000 mother-infant pairs, using Kaiser Permanente hospital records. All of the mothers had undergone a hemoglobin A1c (HbA1c) test—which measures blood glucose levels over a period of months—at some point during the first two trimesters of pregnancy.

The children were followed until they reached four to five years of age. By the end of the follow-up, 707 had received a clinical diagnosis of autism. The researchers report that compared with children whose mothers had an HbA1c of less than 5.7%, children of mothers with an HbA1c greater than 6.5% were nearly twice as likely to receive a diagnosis of autism. The finding is consistent with earlier studies showing that children of mothers with type 1 diabetes, type 2 diabetes, or gestational diabetes diagnosed by the second trimester are at increased odds of developing ASD.

Xiang says, “Maternal diabetes, if not well treated, means hyperglycemia in utero that increases uterine inflammation, oxidative stress, and hypoxia and may alter gene expression. This can disrupt fetal brain development, increasing the risk for neural behavior disorders such as autism.”

The researchers conclude, “Improving glycemic control during pregnancy may reduce the risk of ASD in children, and monitoring HbA1c may assist in identifying at-risk children for early intervention to reduce ASD disabilities.”

“Glycated hemoglobin A1c levels during pregnancy and risk of autism in offspring,” Anny Xiang, Ting Chow, Mayra P. Martinez, Darios Getahun, Kathleen A. Page, Thomas A. Buchanan, and R. Klara Feldman, poster presentation to the American Diabetes Association Scientific Sessions, June 2019. Address: Anny.H.Xiang@kp.org.

—see also—

“Maternal HbA1c influences autism risk in offspring,” healio.com, June 13, 2019.

## Tailored nutritional supplementation improves ASD outcome

Correcting the specific nutritional imbalances of children with autism spectrum disorders (ASD) and supplementing a subgroup of them with folinic acid can significantly improve their symptoms, according to a new study.

Vincent Ramaekers and colleagues assessed the symptoms of 166 children with ASD, none of whom had ASD due to known syndromes, using the Childhood Autism Rating Scale (CARS). They also performed complete blood cell counts on the children and measured their levels of iron, vitamins, coenzyme Q10, metals, and trace elements.

In addition, the researchers tested the children, their parents, and healthy controls for serum autoantibodies directed at the folate receptor alpha (FR $\alpha$ ). These autoantibodies are known to be more common in children with ASD and their families than in the general population, and they can block folate transport from the mother to an unborn child during pregnancy as well as blocking folate transport to the brain in infants (see ARRI 32/1, 2018). The researchers detected FR $\alpha$  autoantibodies in 75.6% of the children, 34.1% of mothers, and 29.4% of fathers, versus 3.3% in controls.

Eighty-two of the children with ASD then underwent a two-year therapeutic trial

designed to address their nutritional imbalances. Those with a positive test for FR $\alpha$  autoantibodies also received high doses of folinic acid (a form of folate that does not require transportation by FR $\alpha$ ). Eighty-four of the children did not receive treatment, and served as controls.

The researchers report, “Compared to untreated patients with autism whose CARS score remained unchanged, a two-year treatment decreased the initial CARS score from severe to moderate or mild autism, achieving complete recovery in 17 of 82 children (20.7%).” Noting that a poorer prognosis correlated with higher FR $\alpha$  autoantibody titers, positive maternal FR $\alpha$  autoantibodies, or FR $\alpha$  autoantibodies in both parents, they suggest that FR $\alpha$  testing of prospective parents, followed by folinic acid supplementation of affected mothers before conception and during pregnancy, may be warranted.

“Improving outcome in infantile autism with folate receptor autoimmunity and nutritional derangements: a self-controlled trial,” Vincent Th. Ramaekers, Jeffrey M. Sequeira, Marco Di-Duca, Géraldine Vrancken, Aurore Thomas, Céline Philippe, Marie Peters, Annick Jadot, and Edward V. Quadros, *Autism Research and Treatment*, June 18, 2019 (free online). Address: Vincent Th. Ramaekers, vramaekers@skynet.be.

## Interoception is impaired in children, but not adults, with ASD

A new study suggests that children, but not adults, with autism spectrum disorders (ASD) have impairments in interoception. Interoception is the ability to sense the internal state of the body—for instance, to accurately identify sensations such as hunger, thirst, pain, and internal temperature.

Research shows that accuracy in identifying interoceptive signals is associated with skill in emotion processing, decision-making, self-regulation, empathy, and theory of mind (the ability to understand that other people have thoughts and feelings). Toby Nicholson and colleagues, the authors of the new study, say, “These wide-ranging associations are in line with theories of embodied cognition that imply cognition is situated in bodily systems, and also point towards a role for interoception in both self and other processing. This has

led to a growing interest in the importance of interoception for disorders such as ASD.”

The researchers say, “The idea is that a difficulty interpreting one’s own internal bodily signals early on may interfere with learning about the association between these low-level bodily signals and other higher-level feelings and thoughts, restricting the comprehension of oneself, which in turn would have similar effects on understanding other selves.”

To test the interoceptive accuracy of individuals with ASD, the researchers performed two experiments. In the first, involving 21 adults with ASD and 21 neurotypical controls, participants completed two tasks. First, they closed their eyes and silently counted the number of heartbeats they felt during

*continued on page 2*

## Pica may largely explain link between autism, GI problems

Pica (the eating of non-food items) may play a significant role in the high rate of gastrointestinal (GI) problems seen in individuals with autism, according to a new study by Dean Alexander and colleagues.

The study, using data collected on developmentally disabled clients at the Lanterman Developmental Center in California, compared four groups of adults:

- Individuals with pica but not autism (16)
- Individuals with autism but not pica (15)
- Individuals with both autism and pica (17)
- A control group of clients matched for gender, age, and level of cognitive functioning (16)

The researchers report, “GI diseases, and signs and symptoms of GI dysfunction, each showed a significant overall effect associated with pica, but not with autism. Those persons diagnosed with pica had 2.8 times as many GI diseases, and 4.8 times as many were severely affected. Persons with pica had 2.6 diseases on average. Additionally, adults with pica showed higher prevalence across all ten most frequently recorded GI diseases.”

They add, “The significant interaction observed in the current study between autism and pica on GI signs and symptoms suggests that it is important to distinguish autism and autism/pica diagnostic groups.” They note that compared to the group with autism alone, the autism/pica group had higher percentages of GERD (35% vs. 7%), vomiting (41% vs 27%), abdominal pain (29% vs 0%), constipation (94% vs. 80%), and alternating diarrhea and constipation (29% vs. 7%).

They conclude, “Our data strongly suggest that the high rate of GI symptoms

*continued on page 6*

### Free Newsletters

In collaboration with the Schafer Autism Report, the Autism Research Institute publishes an e-newsletter titled *Clinical Research in Autism*. This newsletter provides online links to up-to-date clinical research related to patient care, and is designed for pediatricians, nurses, and obstetricians (although other readers are welcome as well). You can subscribe here: <https://www.autism.org/clinical-research-e-newsletter/>

The monthly ARI e-newsletter includes news, webinar updates, and autism-related information and articles. You can subscribe here:

<https://www.autism.org/ari-monthly-e-newsletter/>

## Interoception is impaired in children, but not adults, with ASD (continued from page 1)

specific time intervals. Next, they exhaled into a peak flow meter, attempting to reproduce the intensity of each of three exhalations (weak, medium, and firm). The researchers then repeated the heartbeat experiment with a group of 21 children with ASD and 21 neurotypical children.

The researchers found that children with ASD, but not adults, had significant impairments in interoceptive accuracy. This may suggest, they say, that “a ‘decoupling’ of interoception and emotion processing among some children with ASD results in emotions never being fully anchored within the body, making emotions difficult to understand in self and others across the lifespan even once interoception difficulties have resolved.”

Another possibility, they say, is that “local interoceptive signals are not integrated together in a global sense,” affecting not just emotional processing but also the ability of interoceptive processes to bind with other information sources such as memory and perception. Still a third possibility, they suggest,

is that interoception and theory of mind are independently impaired, which could explain why emotion-processing impairments persist in ASD even after interoceptive impairments have resolved.

“Interoception is impaired in children, but not adults, with autism spectrum disorder,” Toby Nicholson, David Williams, Katie Carpenter, and Aimilia Kallitsounaki, *Journal of Autism and Developmental Disorders*, May 24, 2019 (online). Address: David Williams, D.M.Williams@kent.ac.uk.

## Needs, experiences of sibs of adults with ASD explored

While a number of studies have explored the experiences and needs of parents of adult children with autism spectrum disorders (ASD), a new study by Philippa Moss and colleagues focused instead on siblings. In the study, the researchers asked 37 female and 19 male siblings, averaging 40 years of age, about their experiences growing up with a sibling with autism and their concerns for the future.

More than three-quarters of the participants described benefits related to having a sibling with ASD. Participants frequently mentioned the sibling’s positive characteristics and the beneficial impacts on their own lives or personalities—saying, for example, that growing up with a sibling with ASD made them more tolerant or caring. Only 14% of participants did not cite any benefits to the relationship.

The main problems mentioned by participants were the sibling’s behavior problems and the disruption to the family’s relationships or social life. The researchers detected no association between the level of negative comments about the relationship and participants’ social functioning or mental health.

Two of the biggest concerns expressed by the participants were the need to find appropriate care for siblings with ASD and the potential emotional effect on the siblings when their parents died. The researchers comment, “Most participants described a mix of positive and negative experiences but current concerns focused predominantly on future long-term care. Many adult siblings will become increasingly responsible for ensuring the welfare of the individual with autism. Medical and other services need to recognize the importance of this role, and the need actively to involve siblings in care planning and decision-making.”

“Growing older with autism—the experiences of adult siblings of individuals with autism,” Philippa Moss, Vasiliki Eirinaki, Sarah Savage, and Patricia Howlin, *Research in Autism Spectrum Disorders*, Vol. 63, July 2019, 42-51. Address: Philippa Moss, philippa.moss4@nhs.net.

### The Kids First Initiative: Giving Back to Families

The Hartwell Foundation Kids First initiative seeks to help every family who has a child with an autism spectrum disorder. The goal is to create detailed categories that accurately reflect individual behavior and personality, with the expectation of advancing personalized, targeted approaches for care and intervention that will be more successful than what is available today.

The Kids First approach is conducted using IRB-approved confidential survey methodology by prominent universities. Survey questions are simple, focused on basic behavioral and medical information, and can be completed in about 10 minutes. Results will be shared confidentially with all survey participants. The collected data will provide a unique opportunity for researchers to begin classification of ASD, and as new categories are identified, the effort will expand to more sophisticated requests for information.

We invite you to participate in the Kids First confidential survey, joining a growing network of families, clinicians, and scientists involved in this innovative research project to improve the lives of children and families affected by ASD. To learn more and begin your survey, visit [kidsfirst.stanford.edu](http://kidsfirst.stanford.edu) and when asked, type ARI as your referral code.

**EDITORIAL: Stephen M. Edelson, Ph.D.**

Over the past half-century, two treatment approaches have dominated autism therapy. One is behavioral therapy (for instance, applied behavior analysis), while the other is traditional medical intervention relying largely on medications such as Prozac, Risperdal, Haldol, Tegretol, and Ritalin. Numerous studies support the effectiveness of both approaches.

During this time, other approaches have emerged; however, these approaches have received relatively little attention from researchers in the autism field. They include biomedical interventions (for instance, fecal transplants, methyl B12, and detoxification), nutrition-related health programs, sensory interventions, and communication/speech/language therapies. These treatments are increasingly popular as a result of positive results demonstrated by a modest amount of research as well as benefits seen by parents, teachers, and therapists.

**Is reliance on a single treatment discipline misguided?**

Most behavioral and traditional medical approaches to autism treatment, as well as many alternative treatments, use standardized methods to alleviate symptoms commonly associated with autism. These symptoms include but are not limited to hyperactivity, anxiety, depression, challenging behaviors, and eating and sleeping problems.

Each intervention is highly effective for many children, but less effective (or even ineffective or harmful) for others. This begs the question: Given the heterogeneity of the autism spectrum, which intervention can best treat each symptom?

Today, parents are often urged by professionals to rely on only one treatment approach, or at most two, to help their children. The most typical approaches include behavioral therapy and medications.

Furthermore, clinicians and researchers in the fields of behavioral therapy and traditional medicine frequently raise doubts about the efficacy of other disciplines. Often, this stems from concerns about possible adverse effects, a supposed lack of research on the effectiveness of the approaches, or even hearsay about how the treatments are administered.

However, the assumption that only one or two disciplines will *always* offer the best results across the entire autism spectrum is scientifically unsubstantiated and causes many children with autism to miss out on potentially life-changing interventions. What we need, instead, is a systematic way to determine which approaches will work for each individual child.

**Optimizing Autism Treatment****Multidisciplinary treatment: what is the best approach?**

In comparison to a single treatment approach, a multidisciplinary treatment approach involves identifying symptoms and behaviors of concern and then selecting interventions from various disciplines that are known to effectively treat them.

There are at least two types of multidisciplinary treatment approaches. In one type, treatments presumed to be most effective for each symptom and behavior are included in the treatment plan. For example, this may involve hiring a behaviorist to treat aggression, assigning a sensory therapist to neutralize sensory sensitivities, and having a pediatri-

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The goal for every treatment plan should be to optimize improvement and not to settle for anything less.

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cian or specialist treat activity level, anxiety, and sleep disorders. These recommendations will likely result in improvements, *but they may not be optimal for each individual.*

The second type of approach is an *evidence-based multidisciplinary approach*. This involves assessing symptoms and behaviors of concern with respect to each available treatment discipline. Such an assessment can often provide sufficient information to determine rather precisely how best to treat each symptom and behavior.

This approach may require more time and even incur additional costs, but it is systematic and thorough. *The goal for every treatment plan should be to optimize improvement and not to settle for anything less.*

The evidence-based multidisciplinary approach begins with identifying symptoms and behaviors of concern. This can be done via clinical interviews, direct observations, and/or parent-based questionnaires and checklists, such as the Autism Research Institute's Autism Treatment Evaluation Checklist (ATEC). Next, these symptoms and behaviors are evaluated in greater depth. Many valid questionnaires are available for assessing anxiety, challenging behaviors, GI function, sensory sensitivities and insensitivities, sleep problems, and more. The evaluation can also include laboratory testing and/or a functional behavioral assessment.

Once information regarding the symptoms and behaviors is gathered, other factors can be considered before assigning specific interventions. The possibility of adverse effects may not be acceptable in many cases, especially for those who are medically fragile or emotionally sensitive. For example, specific medications may not be advisable given

that they may exacerbate further constipation in children with gastrointestinal issues. In addition, strict behavioral therapy may not be acceptable to parents with emotionally sensitive children.

Urgency may also be an important factor when deciding which treatments are appropriate. For instance, medication may be the correct choice for an individual with autism who exhibits severe self-injury, even if the recommended medication has potentially serious side effects.

The availability of an intervention (e.g., wait list, distance to the closest referral) should also be a consideration, as well as its affordability (e.g., insurance coverage).

The order of the treatments should also be taken into account. Some interventions may or even should be given simultaneously, whereas others need to be administered in a specific order. For example, a child who is a picky eater should be treated for oral sensitivity prior to starting a nutrition program. Another child who experiences headaches should be treated medically before starting an intense behavior program.

**Clinicians and researchers: a powerful multidisciplinary team**

If clinicians use valid and reliable measures to assess their patients, they can then partner with researchers to evaluate the effectiveness of various interventions in applied real-world settings. Outcome measures should always be assessed objectively to determine whether or not each treatment is, in fact, helpful. Researchers may also want to include direct observation procedures conducted in laboratory or in natural situations.

A relatively large database could be generated from such a coordinated study, involving numerous clinical and research sites. This would allow researchers to formulate statistical algorithms (formulas) to objectively determine an optimal plan for each individual. Specific characteristics of the individual could also be integrated in such algorithms, including age, sex, and other variables found to be relevant in predicting optimal treatment success.

Using such an approach, we could effectively address the wide range of symptoms and behaviors seen across the autism spectrum. As a result, we could minimize trial-and-error and maximize the opportunity for each individual to reach his or her true potential. Thus, I encourage those in the autism treatment community to reconsider their opinions about the value of a multidisciplinary approach—an approach that I strongly believe will help us to better address the needs of the diverse population we serve.

## Research Updates

### Joint attention impaired in infants who develop ASD

Adults with autism spectrum disorders (ASD) show impairments in joint attention—the ability to share a focus on an object or event with another person—and a new study suggests that this problem is already present in infancy.

Pär Nyström and colleagues investigated joint attention skills in 112 10-month-old infants. Eighty-one of the infants were at increased risk for ASD because they had an older sibling with ASD, while 31 were low-risk controls. At follow-up when the children were 36 months old, 22 of the children in the high-risk group had developed ASD.

The researchers tested the infants using activities designed to elicit joint attention. During the activities, they used an eye tracker to determine where the infants looked.

The researchers found, surprisingly, that the infants with ASD did not have impairments in responding to another person's initiation of a joint attention episode. However, they found that rates of initiating joint attention were lower in infants later diagnosed with ASD than in low-risk children or high-risk children who did not develop ASD. In addition, they say, rates of initiating joint attention “followed an atypical developmental trajectory from 10 to 18 months.”

“These results suggest children with autism, as infants, may not themselves create as many opportunities for social learning as other children,” study coauthor Terje Falck-Ytter comments. “The differences were rather subtle, but fully detectable with modern eye tracking technology.” However, he adds, “It is important to note that the results demonstrated significant group differences only, and it is too early to say whether the method can facilitate early detection in a clinical context.”

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“Joint attention in infancy and the emergence

#### ARRI Survey: Seniors with Autism Spectrum Disorder

[https://www.autism.com/adult\\_survey](https://www.autism.com/adult_survey)

We hope the results from this survey will provide insight about the needs and challenges faced by seniors with autism (ages 50 and older) and their support providers, and better inform the autism community, government agencies, and other welfare and health-related organizations about this population's quality of life issues.

of autism,” Pär Nyström, Emilia Thorup, Sven Bölte, and Terje Falck-Ytter, *Biological Psychiatry*, May 2019. Address: Terje Falck-Ytter, [terje.falck-ytter@psyk.uu.se](mailto:terje.falck-ytter@psyk.uu.se).

—and—

“Infants later diagnosed with autism follow adults' gaze, but seldom initiate joint attention themselves,” Elin Bäckström, *Medical Xpress*, May 22, 2019.

### Risk of death in hospital higher for adults with ASD

Adults with autism spectrum disorders (ASD) are more likely than their neurotypical peers to die during a hospital stay, according to a new study.

Ilhom Akobirshoev and colleagues examined the records of more than 34,000 adults with ASD and more than 102,000 age- and sex-matched controls, using data from the 2004-2014 Healthcare Cost and Utilization Project Nationwide Inpatient Sample. The researchers report that adults with ASD were 44% more likely than controls to die during a hospital stay. The risk was greatest for women with ASD, who were more than three times as likely as non-ASD female controls to die in the hospital.

Adults with ASD who died during hospital stays were more likely to have comorbid disorders such as psychoses, other neurological disorders, diabetes, hypothyroidism, rheumatoid arthritis/collagen vascular disease, obesity, weight loss, fluid and electrolyte disorders, deficiency anemias, and paralysis. Surprisingly, the researchers found no elevated risk of in-hospital mortality due to epilepsy in either the ASD group or the controls.

The researchers conclude, “Given our study findings, there is a critical need to improve health care, public health, and social support service interventions and strategies to reduce in-hospital deaths among people with ASD and address medical comorbidities that can potentially be linked to in-hospital deaths. Namely, management and optimization of the most prevalent medical comorbidities that are associated with in-hospital mortality among people with ASD, including psychoses, neurological disorders, and others, should be a priority focus of strategies for improving health care, preventive interventions, and training efforts.”

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“In-hospital mortality among adults with autism spectrum disorder in the United States: a retrospective analysis of US hospital discharge data,” Ilhom Akobirshoev, Monika Mitra, Robbie Dembo, and Emily Lauer, *Autism*, June 12, 2019 (epub prior to print publication). Address: Ilhom Akobirshoev, Brandeis University, 415 South Street, Waltham, MA 02453, [ilhom@brandeis.edu](mailto:ilhom@brandeis.edu).

### Atypical eating habits may raise suspicion for ASD

Atypical eating behaviors may be a sign that children should be screened for autism spectrum disorders (ASD), a new study suggests.

Susan Dickerson Mayes and Hana Zickgraf examined the eating habits of 2,102 children. Of this group, 1,462 children had ASD, 327 had other disorders (for example, ADHD, language disorder, intellectual disability, or learning disability), and 313 were developing typically.

Mayes and Zickgraf assessed the children's eating behaviors using the Checklist for Autism Spectrum Disorder, basing their assessment on parent interviews. They report:

- 70.4% of children with ASD had atypical eating behaviors, compared to 13.1% of children with other disorders and 4.8% of neurotypical children.
- Limited food preferences were the most common issue, followed by hypersensitivity to texture.
- Only children with ASD had pica (the eating of non-food items) or pocketed food without swallowing it.
- The most common preferred foods for 92% of children with ASD who had limited food preferences were grain products and chicken nuggets.

The researchers found that most children with ASD who had atypical eating behaviors exhibited two or more types of issues, and almost a quarter had three or more. In comparison, none of the children with other disorders had three or more issues involving atypical eating.

They conclude, “The number and types of atypical eating behaviors found only in children with autism and not in children with other disorders or typical development should alert clinicians to the possibility of autism and the need to evaluate for autism in order to facilitate early identification and access to evidence-based treatment.”

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“Atypical eating behaviors in children and adolescents with autism, ADHD, other disorders, and typical development,” Susan Dickerson Mayes and Hana Zickgraf, *Research in Autism Spectrum Disorders*, No. 64, August 2019, 76-83. Address: Susan Dickerson Mayes, [smayes@psu.edu](mailto:smayes@psu.edu).

—and—

“Unusual eating behaviors may be a new diagnostic indicator for autism,” Zachary Sweger, *Penn State News*, July 9, 2019.

## Research Updates

### High estrogen levels in utero may raise ASD risk

Exposure to high levels of estrogen before birth may increase the likelihood of autism spectrum disorder (ASD) in males, according to a new study.

In earlier research, Simon Baron-Cohen and colleagues analyzed hormone levels in samples of amniotic fluid from 128 boys later diagnosed with ASD and 217 controls. The researchers found that samples from the boys who developed ASD contained elevated levels of testosterone as well as other hormones that are part of a pathway called the delta-4 sex steroid pathway.

In a new study using amniotic fluid samples from a subgroup of the same children, the researchers analyzed levels of four forms of estrogen—estradiol, estrone, and estrone sulphate. The researchers found that all four forms of estrogen were significantly elevated in the 98 children who later developed autism, compared to the 177 who did not. In fact, the researchers found that high levels of prenatal estrogens were even more predictive of autism than high levels of prenatal androgens such as testosterone.

The researchers note that in both males and females, prenatal estrogen plays a key role in the development of the cerebral cortex and the formation of synapses between neurons in the nervous system. Baron-Cohen comments, “This new finding supports the idea that increased prenatal sex steroid hormones are one of the potential causes for [ASD]. Genetics is well established as another, and these hormones likely interact with genetic factors to affect the developing fetal brain.”

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“Foetal oestrogens and autism,” Simon Baron-Cohen, Alexandros Tsompanidis, Bonnie Auyeung, Bent Nørgaard-Pedersen, David M. Hougaard, Morsi Abdallah, Arieh Cohen, and Alexa Pohl, *Molecular Psychiatry*, July 29, 2019 (online). Address: Simon Baron-Cohen, sb205@cam.ac.uk.

—and—  
“High levels of estrogen in the womb linked to autism,” news release, University of Cambridge, July 29, 2019.

—see also—  
“Linking autism, sex, gender and prenatal hormones,” Simon Baron-Cohen, *Spectrum News*, October 19, 2015.

### Age at which children with ASD walk correlates with severity of symptoms

Children with autism spectrum disorders (ASD) tend to walk later than neurotypical children, and a study from Norway reports

that the age at which children with ASD first walk correlates with the severity of their symptoms.

Lise Reindal and colleagues analyzed data on 490 children clinically evaluated for suspected ASD. They compared the children who received an ASD diagnosis to those who did not, and compared both groups to population norms for children in Norway.

The researchers found that children in the ASD group walked significantly later than those in the non-ASD group, and that later walking was significantly associated with ASD symptom severity. In addition, they report, “Whereas age of first walking was significantly later in males with ASD compared with non-ASD diagnosis, females with autistic symptoms seem to have a liability toward later age of first walking, regardless of ASD diagnosis.”

The researchers comment, “Recognizing that autistic symptoms may be difficult to interpret at an early age, assessing early motor delays and specifically age of first walking may have the potential to improve earlier identification of some cases with ASD, and perhaps particularly in females. Considering the possibility of ASD in infants with motor delays may not only enhance the potential for earlier diagnosis, but also improve the chance of targeting and addressing these delays in treatment programs and facilitate better prognostic outcomes.”

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“Age of first walking and associations with symptom severity in children with suspected or diagnosed autism spectrum disorder,” Lise Reindal, Terje Naerland, Bernhard Weidle, Stian Lydersen, Ole A. Andreassen, and Anne Mari Sund, *Journal of Autism and Developmental Disorders*, July 5, 2019 (free online). Address: Lise Reindal, Department of Child and Adolescent Psychiatry, Møre og Romsdal Hospital Trust, Volda Hospital, Pb 113, 6101, Volda, Norway, lise.reindal@ntnu.no.

#### — AUTISM.JOBS —

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### More evidence seen for relationship between GI symptoms, behavior issues

A study from the University of Missouri adds to evidence that behavior problems in children with autism spectrum disorders (ASD) can be an indication of gastrointestinal (GI) distress.

Bradley Ferguson and colleagues analyzed records from 340 children and adolescents with ASD. The researchers found that 65% of the individuals experienced constipation, nearly half experienced stomach pain, nearly 30% experienced diarrhea, and 23% experienced nausea. They also detected an association between some GI problems and behavioral issues such as anxiety and aggression.

Ferguson comments, “We are starting to better understand how gastrointestinal issues coincide with problem behaviors in ASD. For example, we found that individuals with autism and co-occurring nausea were about 11% more likely to display aggressive behaviors. Therefore, addressing the nausea might alleviate the aggressive behaviors which will ultimately increase the quality of life for the patient as well as their family.”

The researchers also discovered differences between younger and older children with ASD. For instance, aggressive behavior in very young children was associated with upper GI issues such as nausea and stomach pains, while anxiety in older children and teens was associated with lower GI issues such as constipation and diarrhea.

Ferguson says, “These findings further highlight the importance of treating gastrointestinal issues in autism. Many children and adolescents with autism spectrum disorder are often unable to verbally communicate their discomfort, which can lead to problem behavior as a means of communicating their discomfort.”

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“The relationship among gastrointestinal symptoms, problem behaviors, and internalizing symptoms in children and adolescents with autism spectrum disorder,” Bradley J. Ferguson, Kristen Dvogan, Nicole Takahashi, and David Q. Beversdorf, *Frontiers in Psychiatry*, April 9, 2019 (free online). Address: Bradley J. Ferguson, fergusonbj@health.missouri.edu.

—and—  
“Problem behaviors could provide clues on health challenges for children, adolescents with autism,” news release, University of Missouri, June 27, 2019.

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## Case study indicates that oral contraceptives may help reduce pica in some females with ASD

Oral contraceptives may help to reduce pica (the eating of non-food items) in some females with autism spectrum disorders (ASD), according to a new case report by Harris Wild and Russell Tobe.

The authors' patient, a 17-year old female with ASD and a near-normal IQ, had exhibited pica since the age of 6 months. Her pica included eating sand, rocks, clothing, electrical insulation, and the metal eraser holders on pencils. Evaluation indicated that the pica did not result from discomfort, and the girl's lab tests were normal.

Due to her pica, the girl required a one-on-one school aide. She began taking sertraline for anxiety when she was 11 years of age, but while this reduced her anxiety, it did not affect her pica.

When the girl began having menstrual periods, the frequency of her pica incidents increased immediately before her periods, returning to baseline when they ended. When she began taking an oral contraceptive at the age of 16, the rise in pica incidents prior to her periods no longer occurred, and her levels of pica across all menstrual phases dropped below her pre-puberty levels.

### Pica may largely explain link between autism, GI problems (continued from page 2)

observed among people with autism can be accounted for by pica... Indeed, individuals with both autism and pica may be a phenotypic subgroup."

The researchers say, "From a behavior-analytic viewpoint, we conceptualize pica here primarily as part of a chain of events: (1) persistent exploratory mouthing of environments (sensory reinforcement), (2) introduction into the gut of harmful bacteria, the metabolites of which may affect the body and brain, (3) maldigestion and malabsorption or faulty metabolism, (4) nutritional deficiencies, (5) pica disorder, (6) GI symptomatology, (7) GI disease."

The researchers suggest that nutritional deficiencies and imbalance help to set the stage for pica, and recommend that individuals with pica receive nutritional and gastrointestinal evaluation.

"Gastrointestinal tract symptomatology in adults with pica and autism," Dean D. Alexander, Stanley E. Lunde, and Dale E. Berger, unpublished paper. Address: Dale E. Berger, Department of Psychology, Claremont Graduate University, 123 East Eighth Street, Claremont, CA 91711, dale.berger@cgu.edu.

**Editor's note: While we typically review only published papers, we chose to make an exception in this case because of the importance of these findings.**

Women on oral contraceptives typically take placebo pills for one week during each menstrual cycle. In this case, Wild and Tobe say, the switch from the contraceptive pills to the placebo pills resulted in a recurrence of pica within 24 to 48 hours.

"At age 17 years," the authors say, "the frequency of the placebo week was reduced from monthly to quarterly, with near remission of pica behavior. The school-based aide was discontinued."

Wild and Tobe say that while oral contraceptives may have reduced menstrual

discomfort, this would not explain the reduction in pica at other times of the month. Alternatively, they say, the improvements may have stemmed from the effects of estrogen on serotonin levels in the central nervous system.

"Oral contraceptives reduced pica behavior in a female with autism spectrum disorder," Harris Wild and Russell H. Tobe, *Journal of Child and Adolescent Psychopharmacology*, July 24, 2019. Address: Russell H. Tobe, Nathan Kline Institute for Psychiatric Research, 140 Old Orangeburg Road, Office N 106, Orangeburg, NY 10962, russell.tobe@NKL.rfmh.org.

## ASD, moms' job exposure to solvents: is there an association?

Exposure to solvents may increase a pregnant woman's risk for having a child with an autism spectrum disorder (ASD), according to a new study.

Erin McCanlies and colleagues analyzed data from the CHildhood Autism Risks from Genetics and Environment (CHARGE) study. The data included personal, health, and job history information for the parents of 537 children diagnosed with autism spectrum disorders and 414 neurotypical children.

Industrial hygienists calculated the intensity and frequency of the parents' occupational exposure to 16 agents linked to neurological or congenital abnormalities. These included medicines, metals, pesticides, anesthetics, asphalt, brake fluid, plastics and polymers, radiation, cleaners/disinfectants, and solvents (including paints and degreasers as well as other chemicals). The researchers focused on parental exposures occurring from three months pre-pregnancy until birth. They

classified exposures as none; rare (a few times a year); moderate (weekly); and frequent (several times a week or daily), and categorized intensity as low, moderate, or high.

The researchers report, "The adjusted odds ratio of ASD in the children of mothers exposed to any solvents was 1.5 times higher than the mothers of TD children. Cumulative exposure indicated that the adjusted odds ratio associated with a moderate level of solvent exposure in mothers was 1.85 for children with ASD compared with TD children. No other exposures were associated with ASD in mothers, fathers or the parents combined."

The researchers note that while their study shows a possible association between maternal exposure to solvents and ASD in children, it does not prove that solvents cause ASD. They add that their results should be interpreted with caution because the association between ASD and maternal solvent exposure was no longer significant after the researchers corrected for statistical bias. "However," they say, "these results are consistent with earlier reports that have identified solvents as a potential risk factor for ASD."

Unlike a number of earlier studies, this study did not detect a relationship between parental occupational exposure to metals or pesticides and ASD. The researchers say this may be due to the small number of participants who had significant exposure to metals or pesticides.

"The CHARGE study: an assessment of parental occupational exposures and autism spectrum disorder," Erin C McCanlies, Claudia C Ma, Ja Kook Gu, Desta Fekedulegn, Wayne T Sanderson, Yunin J Ludeña-Rodríguez, and Irva Hertz-Picciotto, *Occupational and Environmental Medicine*, June 27, 2019 (epub prior to print publication). Address: Erin McCanlies Health Effects Laboratory, National Institute for Occupational Safety and Health, Morgantown, WV 26505, eim4@cdc.gov.

"Mum's workplace exposure to solvents may heighten child's autism risk," news release, *British Medical Journal*, June 27, 2019.

### Participants needed for ASD microbiome study

Researchers at Massachusetts General Hospital, Harvard Medical School, and the Autism Research Institute are investigating whether the reason why boys are more affected than girls is related to differences in intestinal bacteria.

We are seeking families to participate in this study who have boy and girl siblings with autism. These families will be mailed stool kits with instructions and will be asked to collect samples. A brief medical history will be taken.

For additional information and enrollment details, please contact Harland Winter, MD by phone at 617-724-2004 or by email at GenderDimorphism@autism.com.

## Common food additive damages brain cells, may play role in autism spectrum disorders

A commonly used food preservative may play a role in autism spectrum disorders (ASD), according to a new study.

The preservative, propionic acid (PPA), is used to increase the shelf life of packaged foods and inhibit mold in commercially processed cheese and bread. Latifa Abdelli and colleagues note that while PPA is also produced naturally by the body, eating foods high in PPA can lead to increased gut levels in pregnant women that can cross to the fetus.

The researchers point out that elevated levels of PPA have been found in the stools of individuals with ASD. Additionally, they note that a disorder called propionic acidemia (PA), which causes PPA to accumulate in the blood, causes symptoms including seizures, movement disorders, gastrointestinal issues, aloofness, and overall developmental delays. “Interestingly,” they say, “PA and ASD share most of their core symptoms with multiple case studies reporting ASD as a comorbidity to PA.” The researchers also note that PPA

is believed to cause mitochondrial dysfunction, a problem that affects more than 30% of individuals with ASD.

To explore the effects of elevated PPA on the developing brain, the researchers exposed neural stem cells to excessive PPA and discovered that this exposure damages brain cells in two ways:

- It disrupts the natural balance between brain cells by reducing the number of neurons and causing gliosis (an overproduction of glial cells). This excess of glia cells alters connectivity between neurons and causes inflammation.
- It shortens and damages pathways that neurons use to communicate with the rest of the body.

The researchers say these effects impair the brain’s ability to communicate and could result in behaviors that are often seen in children with ASD, including repetitive behavior, mobility issues, and an inability to interact with others.

They conclude, “Clearly, the data supports a significant role for PPA in modulating human neural stem cell patterning leading to gliosis, disturbed neuro-circuitry, and inflammatory response as seen in ASD.” However, they say more research is needed to clarify the possible relationship between PPA and ASD. Their next step, they say, will be to see if a maternal diet high in PPA causes autism in mice genetically predisposed to the condition.

—  
 “Propionic acid induces gliosis and neuroinflammation through modulation of PTEN/AKT pathway in autism spectrum disorder,” Latifa S. Abdelli, Aseela Samsam, and Saleh A. Naser, *Nature Scientific Reports*, June 19, 2019 (free online). Address: Saleh A. Naser, Burnett School of Biomedical Sciences, College of Medicine, University of Central Florida, Orlando, FL 32816, Saleh.Naser@ucf.edu.

—and—  
 “Processed foods may hold key to rise in autism,” news release, University of Central Florida, June 20, 2019.

### Free Autism Continuing Education and Webinars

Free Certificates of Participation are available upon passing an online quiz for most webinars. Some events offer Continuing Education Units and/or Continuing Medical Education credits.

October 23, 2019  
 10:00-11:00 a.m. MST  
**FRAGILE X AND ASD**  
 Randi Hagerman, M.D.

November 6, 2019  
 11:00 a.m.-noon MST  
**PANS/PANDAS—RESEARCH UPDATE**  
 Sue Swedo, M.D.

November 27, 2019  
 11:00 a.m.-noon MST  
**SENSORY PROCESSING AND ASD**  
 Virginia Spielmann, MSOT

January 13, 2020  
 11:00 a.m.-noon MST  
**GENE-ENVIRONMENT INTERACTIONS IN ASD:  
 RESEARCH UPDATES**  
 Valerie W. Hu, Ph.D.

March 4, 2020  
 11:00 a.m.-noon MST  
**GASTROINTESTINAL ISSUES & ASD**  
 Kara Gross-Margolis, M.D.

Space is limited—watch your email, or visit us on Facebook and Twitter for updates and registration links. You can view previous webinars in our archives at <https://www.autism.com/webinars>.

\* We are grateful to our friends at the Johnson Center for Child Health & Development for working in partnership to offer presentations.

### Quotable...

“Companies have experienced a surprising array of benefits from neurodiversity programs. Some are straightforward: Firms have become more successful at finding and hiring good and even great talent in tough-to-fill skills categories. Products, services, and bottom lines have profited from lower defect rates and higher productivity. Both SAP and HPE [Hewlett Packard Enterprise] report examples of neurodiverse employees’ participating on teams that generated significant innovations (one, at SAP, helped develop a technical fix worth an estimated \$40 million in savings).

“Other benefits are subtler. One executive told us that efforts to make corporate communications more direct, in order to account for the difficulties autistic employees have with nuance, irony, and other fine points of language, have improved communication overall. The perfectionist tendencies of some HPE software-testing pods have caused client organizations to raise their game and stop viewing certain common problems as inevitable. In addition, employee engagement has risen in areas the programs touch: Neurotypical people report that involvement makes their work more meaningful and their morale higher. And early indications suggest that program employees, appreciative of having been given a chance, are very loyal and have low rates of turnover.”

Robert D. Austin and Gary P. Pisano,  
 “Neurodiversity as a  
 Competitive Advantage,”  
 Harvard Business Review, 2017

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