2017 SUMMARY OF ADVANCES in Autism Spectrum Disorder Research

INTERAGENCY AUTISM COORDINATING COMMITTEE
2017
SUMMARY OF ADVANCES
in Autism Spectrum Disorder Research
COVER DESIGN
NIH Medical Arts Branch

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ABOUT THE IACC

The Interagency Autism Coordinating Committee (IACC) is a Federal advisory committee charged with coordinating Federal activities concerning autism spectrum disorder (ASD) and providing advice to the Secretary of Health and Human Services (HHS) on issues related to autism. The Committee was established by Congress under the Children’s Health Act of 2000, reconstituted under the Combating Autism Act (CAA) of 2006, and renewed most recently under the Autism Collaboration, Accountability, Research, Education, and Support (CARES) Act of 2014.

Membership of the Committee includes a wide array of Federal agencies involved in ASD research and services, as well as public stakeholders, including self-advocates, family members of children and adults with ASD, advocates, service providers, and researchers, who represent a variety of perspectives from within the autism community. The IACC membership is composed to ensure that the Committee is equipped to address the wide range of issues and challenges faced by individuals and families affected by autism.

Under the CAA and subsequent reauthorizations, the IACC is required to (1) develop and annually update a strategic plan for ASD research, (2) develop and annually update a summary of advances in ASD research, and (3) monitor Federal activities related to ASD.

Through these and other activities, the IACC provides guidance to HHS and partners with other Federal departments, Federal agencies, research and advocacy organizations, and the broader autism community to accelerate research and enhance services with the goal of profoundly improving the lives of people with ASD and their families.

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For more information about the IACC, see http://www.iacc.hhs.gov.
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INTRODUCTION

THE 2017 IACC SUMMARY OF ADVANCES IN AUTISM SPECTRUM DISORDER RESEARCH

Each year, the IACC releases a list of scientific advances that represent significant progress in the field. The 2017 Summary of Advances provides short, plain language summaries of the top research breakthroughs selected by the IACC from a pool of research articles nominated by the members. The 20 studies selected for 2017 have provided new insight into potential biomarkers to predict risk of autism spectrum disorder (ASD), developmental trajectories of children with ASD, and the impact of various prenatal exposures on ASD risk. The advances also include studies that investigated treatments and interventions for both ASD and co-occurring conditions, the impact of policy changes on ASD health care spending, patterns of injury mortality, and prevalence differences across demographic groups. Articles in the IACC Summary of Advances are grouped according to the topics represented by the seven questions of the 2016-2017 IACC Strategic Plan for ASD. Citations for the articles selected for the Summary of Advances, as well as a complete listing of those nominated, are included at the end of the document.
ARTICLES SELECTED FOR THE 2017 SUMMARY OF ADVANCES

QUESTION 1: HOW CAN I RECOGNIZE THE SIGNS OF ASD, AND WHY IS EARLY DETECTION SO IMPORTANT?

• Race influences parent report of concerns about symptoms of autism spectrum disorder
• Functional neuroimaging of high-risk 6-month-old infants predicts a diagnosis of autism at 24 months of age
• Early brain development in infants at high risk for autism spectrum disorder
• A prospective study of the concordance of DSM-IV and DSM-5 diagnostic criteria for autism spectrum disorder

QUESTION 2: WHAT IS THE BIOLOGY UNDERLYING ASD?

• Infant viewing of social scenes is under genetic control and is atypical in autism
• What will my child’s future hold? Phenotypes of intellectual development in 2-8-year-olds with autism spectrum disorder

QUESTION 3: WHAT CAUSES ASD, AND CAN DISABLING ASPECTS OF ASD BE PREVENTED OR PREEMPTED?

• Cross-tissue integration of genetic and epigenetic data offers insight into autism spectrum disorder
• Fetal and postnatal metal dysregulation in autism
• Prenatal exposure to fever is associated with autism spectrum disorder in the Boston Birth Cohort
• Maternal multivitamin intake, plasma folate and vitamin B12 levels and autism spectrum disorder risk in offspring
• Autism risk following antidepressant medication during pregnancy
• The association between maternal use of folic acid supplements during pregnancy and risk of autism spectrum disorders in children: a meta-analysis

QUESTION 4: WHICH TREATMENTS AND INTERVENTIONS WILL HELP?

• Adaptive behavior in autism: minimal clinically important differences on the Vineland-II
• A randomized, placebo-controlled trial of metformin for the treatment of overweight induced by antipsychotic medication in young people with autism spectrum disorder: open-label extension
• Parent-delivered early intervention in infants at risk for ASD: effects on electrophysiological and habituation measures of social attention

QUESTION 5: WHAT KINDS OF SERVICES AND SUPPORTS ARE NEEDED TO MAXIMIZE QUALITY OF LIFE FOR PEOPLE ON THE AUTISM SPECTRUM?

• Effects of state insurance mandates on health care use and spending for autism spectrum disorder
• Cost offset associated with Early Start Denver Model for children with autism

QUESTION 6: HOW CAN WE MEET THE NEEDS OF PEOPLE WITH ASD AS THEY PROGRESS INTO AND THROUGH ADULTHOOD?

• Injury mortality in individuals with autism

QUESTION 7: HOW DO WE CONTINUE TO BUILD, EXPAND, AND ENHANCE THE INFRASTRUCTURE SYSTEM TO MEET THE NEEDS OF THE ASD COMMUNITY?

• Autism spectrum disorder among US children (2002-2010): socioeconomic, racial, and ethnic disparities
• What is the male-to-female ratio in autism spectrum disorder? A systematic review and meta-analysis
How can I recognize the signs of ASD, and why is early detection so important?

The average age of diagnosis of ASD in the U.S. is 4 years old, but most parents first report concerns about behavior much earlier, during the first two years of the child’s life. Early ASD diagnosis is important because it facilitates earlier intervention that may help children make greater gains in their skills and functioning by school age. However, racial disparities exist for children receiving an ASD diagnosis; Black children are generally diagnosed later in life than White children. There have been few studies to examine the possible reasons for this difference in diagnosis.

Parent report of concerns may be an important factor in early diagnosis. Studies show that Black parents are more likely than White parents to report concerns about disruptive behaviors but are less likely than White parents to report concerns about autism symptoms, which raises the question of whether Black parents sometimes observe ASD symptoms but report them as behavioral problems. Additionally, research has suggested that Black children are twice as likely to receive a misdiagnosis from a clinician before receiving an ASD diagnosis. The goal of this study was to investigate the differences in which Black and White parents report concerns about their children’s behavior and development as related to ASD symptoms. The researchers aimed to determine if fewer reported concerns by Black parents about ASD symptoms might be a contributing factor to the age difference in ASD diagnoses among Black and White children.

The study included 174 children with ASD between 18 and 40 months old, and their parents. The children were screened for ASD or pervasive developmental disorder not otherwise specified (a developmental disorder that is related to ASD). Prior to screening the children, the researchers asked the parents to fill out a free-response questionnaire describing their child’s development. Parent concerns were categorized into two groups: ASD concerns (which included speech/communication, restricted and repetitive behavior, social deficits, and directly naming autism) and non-ASD concerns (which included motor difficulties, behavior/temperament, medical/regulatory, general development, feeding/eating, and disruptive behavior).
The researchers found that Black parents reported fewer ASD concerns than did White parents, but that Black and White parents were equally likely to report non-ASD concerns. Among parents who reported ASD concerns, White parents were far more likely than Black parents to report a social or restricted and repetitive behavior concern. However, there were no significant differences in the likelihood to report speech concerns or to specifically mention autism. Among those who reported non-ASD concerns, Black parents and White parents were equally likely to report disruptive behavior, contradicting previous research that suggested that Black parents are more likely to report disruptive behavior.

The results of this study indicate that Black parents are less likely to report concerns about social behavior and restricted and repetitive behavior, which could be one contributing factor to a missed or delayed diagnosis by a clinician. The researchers suggest that future studies should examine if a lack of reported concerns is related to access to information about ASD symptoms among Black parents. Improving parents' knowledge of and ability to communicate about ASD symptoms may be an area that can be targeted to reduce the current disparities in age difference at time of diagnosis.

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ASD symptoms in young children are often evident by 24 months of age, but often children are diagnosed much later. Research has suggested that detection and intervention before 24 months of age can improve skills and abilities in children with ASD. Although infants as young as 6 months old can display behavioral differences that are related to ASD or other developmental disabilities, these behavioral signs are not strong or specific enough to predict an ASD diagnosis or differentiate it from other types of developmental delays. In this study, researchers used functional connectivity magnetic resonance imaging (fcMRI) to look at the brain connectivity of 6-month-old infants who had high familial risk of developing ASD (children with a high familial risk have about a 20% chance of developing ASD as compared to about a 1.5% chance for the general population). The goal of the study was to determine whether early fcMRI findings could predict a later ASD diagnosis at 24 months.

First, the researchers performed fcMRIs on 59 infants at 6 months old. Using an analysis of different brain regions, brain connections, and the relationship of those brain regions and connections to behaviors, the researchers identified areas of interest and used the analysis to develop a method to predict an ASD diagnosis. Later, when the infants reached 24 months old, the researchers tested the infants for ASD based on their social behavior, language, motor development, and repetitive behavior. They compared their ASD predictions from the fcMRI scans at 6 months with the outcomes of ASD diagnostic testing at 24 months.

Based on the testing at 24 months, 11 children received an ASD diagnosis. Of those 11 children, 9 diagnoses were correctly predicted by the fcMRI that was performed when the children were 6 months old. Likewise, all 48 children who did not receive an ASD diagnosis at 24 months were correctly predicted to test negative for ASD based on their fcMRI scans at 6 months old. Further, of the 26,335 neural connections studied from the fcMRI scan, the researchers identified 974 connections that differ between ASD and non-ASD children. Importantly, neural activity that was recorded in the brain regions of interest during the fcMRI scans corresponded with the behavioral differences that were observed in children at 24 months old.

The researchers conclude that neuroimaging at 6 months of age can accurately predict an ASD diagnosis, with greater than 96% accuracy. Recognizing, however, that diagnostic fcMRIs are too expensive to be widely used as ASD screening tools, the researchers suggest that future studies build on these findings to continue the development of more cost-effective early diagnostic methods.

**Functional neuroimaging of high-risk 6-month-old infants predicts a diagnosis of autism at 24 months of age**

Brain enlargement has been observed in children with ASD, and evidence suggests that changes in brain volume can be observed between 12 and 24 months of age. In this study, the researchers sought to determine whether changes in the brain volume of children younger than 24 months of age correspond with the onset of behavioral symptoms of ASD.

The researchers used a subset of data from an existing study, which consisted of 106 infants with high familial risk of developing ASD and 42 infants with low familial risk. The researchers used behavioral assessments and magnetic resonance imaging (MRI) to evaluate the infants for ASD at 6, 12, and 24 months of age. After the evaluation at 24 months, the researchers divided the participants into three groups: those with high familial risk who screened positive for ASD (HR-ASD), those with high familial risk who screened negative for ASD (HR-neg), and low-risk infants who screened negative for ASD (LR).

The researchers looked at the rate at which total brain volume (TBV) increased between 6 and 12 months of age and between 12 and 24 months of age. They found that the TBV growth rate between 12 and 24 months was significantly higher in the HR-ASD group than in the HR-neg or the LR group. No such difference was seen among the groups between 6 and 12 months of age. However, for infants diagnosed with ASD at 24 months, the increase in TBV was correlated with hyper-expansion of the surface area of the outer layer of the brain, called the cerebral cortex, in the first year of life.

The researchers next looked to see if the TBV growth rate corresponded with ASD severity to determine if faster growth rate indicates more severe ASD behavioral symptoms. They compared the change in TBV growth rate between 6 and 12 months and between 12 and 24 months with the Autism Diagnostic Observation Schedule (ADOS) score administered to the children at 24 months. The ADOS measures two types of behavioral domains: 1) Social Affect, which measures behaviors such as social gestures and eye contact and 2) Restricted and Repetitive Behaviors, which measures behaviors such as hand flapping, rituals, or sensory sensitivities. They found a significant relationship with the change in TBV growth rate between 12 and 24 months and the severity of symptoms in children measured by the ADOS score. The strongest correlation was between TBV growth rate and the ADOS Social Affect score, such that faster TBV growth was associated with a reduced number of typical social behaviors.

**Early brain development in infants at high risk for autism spectrum disorder**

Lastly, the researchers determined whether specific brain measurements taken at 6 and 12 months of age could predict a positive ASD diagnosis at 24 months of age. They examined the change in cortical thickness (a measure of the thickness of the outer layer of the brain) and cortical surface area (a measurement of the folds in the outer layer of the brain) in HR-ASD and HR-neg infants between 6 and 12 months of age. They found that the rate at which cortical surface area increased was significantly higher in HR-ASD infants than in HR-neg infants. The greatest increase occurred in areas of the brain that control sensory information processing. This finding suggests that changes in brain growth rate between 6 and 12 months of age can predict changes in the brain that occur between 12 and 24 months of age and correspond with the development of ASD symptoms.

Together, these results provide potential predictive and diagnostic measures of the development of ASD, and shed light on the physical changes that correspond with behavioral differences during the critical period of ASD symptom emergence and diagnosis.
The Diagnostic and Statistical Manual of Mental Disorders (DSM) is a tool used to diagnose mental health disorders that is periodically updated to revise diagnostic criteria. ASD has been included in the DSM since the third edition (DSM-III) was released in 1980. The most recent revision from DSM-IV to DSM-5 has been met with some controversy. Specifically, the DSM-IV included subcategories of autism, including autistic disorder, pervasive developmental disorder not otherwise specified (PDD-NOS), and Asperger’s disorder. Revisions to the DSM-5 merged the subcategories of autism under a single category of ASD and changed parts of the diagnostic criteria.

The goal of this study was to compare the ASD diagnostic criteria of the DSM-IV and the DSM-5 to determine how changes in categories and criteria could affect the calculation of autism rates and inclusion in autism research. The participants were 439 children and adolescents who had previously been referred for a diagnostic evaluation for autism. Some of the children met diagnostic criteria for ASD based on the DSM-IV, the DSM-5, or both. Some of the children did not meet the criteria for ASD based on either version. Following several diagnostic assessments, clinicians completed a DSM-IV and DSM-5 checklist for each child to determine if the child met the criteria for ASD based on both versions of the DSM.

Of the 439 children evaluated, 278 met DSM-IV criteria for ASD (229 met criteria for autism, 25 met criteria for Asperger’s, and 24 met criteria for PDD-NOS), and 249 children met DSM-5 criteria. Thirty children met DSM-IV but not DSM-5 criteria, and one child met DSM-5 but not DSM-IV criteria. Of those that met DSM-IV but not DSM-5 criteria, 3% met criteria for autism, 20% met criteria for Asperger’s, and 75% met criteria for PDD-NOS.

The researchers performed statistical tests to compare the sensitivity (the ability of the diagnostic test to correctly identify people with ASD) and the specificity (the ability of the diagnostic test to correctly identify people without ASD) of the DSM-5 relative to the DSM-IV. They found that the DSM-5 showed near-perfect specificity (0.99) and a relatively high sensitivity (0.89) for ASD overall, and that both sensitivity and specificity were strongest for children who met criteria for autistic disorder. The DSM-5 was less sensitive for children with Asperger’s, and significantly less sensitive for children with PDD-NOS. Similarly, the DSM-5 was about half as specific for correctly identifying a child that does not have Asperger’s and PDD-NOS.
The researchers also looked at whether demographic factors, such as age, race, gender, intelligence scores, and parental education level affect the level of agreement between DSM-IV and DSM-5 diagnoses. They found that higher scores on intelligence tests were associated with discordance, or mismatching, of the DSM-5 criteria with the DSM-IV criteria. They also found that discordance was more likely between the two versions when assessing girls, highlighting the existing concern that females with ASD are under-identified.

The researchers concluded that the DSM-5 criteria are stricter than the DSM-IV criteria, particularly for diagnosis of Asperger’s and PDD-NOS, and that more subtle symptoms may be less likely to meet criteria. However, they also propose that the more stringent criteria established in the DSM-5 may result in more consistent diagnoses across clinicians, which may help ensure that services and support are better matched.
Social visual engagement — visual attentiveness and engagement with social cues — is one of the earliest observable actions of infants and plays an important role in how infants learn to socially interact with others. Children with ASD frequently display impairment of social visual engagement, a deficit that can be detected as early as the first six months of life. There is evidence that ASD is heritable, but the mechanisms of genetic influence on development and behaviors are not well understood. To better understand the social development of children with ASD, it is important to investigate the genetic factors that influence social visual engagement.

In this study, researchers performed eye-tracking experiments on a group of 338 toddlers, consisting of 82 identical twins, 84 fraternal twins, 88 non-twins with ASD, and 84 non-related controls. By comparing groups of toddlers 18-24 months of age who were either genetically identical (identical twins), genetically similar (fraternal twins), or genetically unrelated (non-related controls and non-related children with ASD), the researchers were able to investigate whether responses to social cues are genetically determined. They did so by measuring patterns of the toddlers’ visual responses to videos that mimic typical social situations.

First, the researchers presented the videos to identical twins, fraternal twins, and non-related controls. As the toddlers watched the social interactions presented in the video, specialized equipment tracked their eye movements. The researchers used these measurements to track the speed with which toddlers looked toward faces and the amount of time the toddlers gazed at the eye and mouth regions, specifically to determine concordance—the probability that the two individuals share a trait or characteristic. They found that identical twins had the greatest concordance of their visual responses to both eye and mouth stimuli: 91% of the time, they responded similarly to each other when observing eye stimuli, and 86% of the time when observing mouth stimuli. Fraternal twins showed modest concordance with 35% concordance for eye and 44% concordance for mouth stimuli, and
non-related controls showed no concordance in their visual responses. Since identical twins are more genetically similar than fraternal twins, a higher level of concordance in identical twins indicates that visual engagement is highly heritable.

Identical twins also showed greater concordance in the amount of time spent looking at facial features than they did in the amount of time spent looking at other non-social objects in the videos. Fraternal twins and non-related controls did not show a significant difference in concordance when looking at social versus non-social aspects of the videos.

Next, the researchers looked at the timing and direction of eye movements of the three groups. Identical twins were more likely to move their eyes at the same time in response to social stimuli than fraternal twins or non-siblings. Further, identical twins were more likely to move their eyes in the same general direction than were fraternal twins. The researchers also considered timing and direction together and found that identical twins were more likely than fraternal twins to look in the same direction at the same time. Together, these results indicate that the level of concordance of responses to social visual stimuli was highest for the genetically identical toddlers, suggesting that social visual engagement is linked to genetic factors.

Lastly, the researchers compared visual responses of typically developing identical twins, fraternal twins, and non-siblings with those of toddlers with ASD. They found that the toddlers with ASD showed reduced responses to the social aspects of the videos. Based on their findings that social visual engagement is genetically determined, they suggest that genetic differences in children with ASD underlie their differences in social behavior compared to their typically-developing peers.
QUESTION 2: WHAT IS THE BIOLOGY UNDERLYING ASD?

What will my child's future hold? Phenotypes of intellectual development in 2-8-year-olds with autism spectrum disorder

The severity of ASD is highly variable, and currently, little is known about the relationship between symptoms that present early in life and long-term outcomes. Intellectual ability, typically assessed by intelligence quotient (IQ), can serve as a strong outcome predictor for children with and without ASD. Although recent literature has investigated the relationship between ASD and IQ, no studies have identified the different ways IQ can change over the course of a child's development, nor how these trajectories affect ASD outcomes.

In this study, researchers presented four hypotheses related to intellectual ability and ASD outcomes, hypothesizing that: 1) their findings would support previous research, which suggests that there are four different IQ trajectories for children with ASD from two to eight years old; 2) only the small proportion of children who lose their ASD diagnoses by eight years old would be more likely to have higher IQs at two years old, while IQ would not be significantly related to ASD symptom severity in children who don't lose their diagnoses; 3) children who had the greatest increases in IQ would have relatively higher non-verbal abilities at age 2 and show strong adaptive communication development from age 2 to 8; and 4) children who showed increases in IQ would demonstrate low levels of internalizing behaviors, such as anxiety, depression, and complaints of physical ailments.

To test these hypotheses, the researchers tracked changes in intellectual ability for 102 children with and without ASD over the course of early (ages 2-3.5) and middle (ages 5-8) childhood. Using a combination of scores obtained during assessments at both timepoints, the researchers estimated and compared IQ at both time points. For some children, IQ either increased or decreased between the two timepoints; for others, IQ remained stable. Addressing their first hypothesis, the researchers identified four different developmental trajectories for children with ASD, based on these changes in IQ:

- The “High Challenges” group constituted about a quarter (25.5%) of the participants. These children had the lowest average IQ at baseline, and their IQs declined over time.
- The “Stable Low” group had a low and steady IQ, not significantly increasing or decreasing between the two timepoints. This group comprised 17.6% of the children who participated.
- The “Changers” group, slightly more than a third (35.3%) of the children, showed significantly improved IQ scores between the two timepoints.
- The “Lesser Challenges” group, which included 21.6% of the children who participated, had the highest average IQ at baseline. The children in this group had IQ scores that were close to the average IQ of non-ASD children at both time points.
Supporting their second hypothesis, the researchers found that 14% of children in the Lesser Challenges group and 6% of children in the Changers group no longer met criteria for ASD at the second timepoint. Confirming the researchers third hypothesis, children with the greatest increase in IQ (the Changers group), exhibited such significant improvements in their communication abilities by the second timepoint that they were essentially equivalent to children in the Lesser Challenges group. The Stable Low group also showed some increase in their communication abilities, but the severity of their ASD symptoms also increased with time. Finally, contrary to their fourth hypothesis, all four trajectory groups had similar baselines and all demonstrated a similar decline in internalizing behaviors over time. Importantly, they found that none of the groups differed in the amount of interventions they had received.

The results of this study are hopeful, as more than 30% of children showed dramatic increases in IQ over time and 5% no longer met criteria for ASD at the second timepoint. The study is ongoing, and future examination of these children will provide more insight into the long-term trajectory of each of these groups.
WHAT CAUSES ASD, AND CAN DISABLING ASPECTS OF ASD BE PREVENTED OR PREEMPTED?

Cross-tissue integration of genetic and epigenetic data offers insight into autism spectrum disorder

Development of ASD is thought to be due in part to genetic factors. Although no single genetic variation has been discovered that is sufficient to cause ASD, current research has provided some insight into variations in gene expression and modifications that are associated with increased ASD risk. In this study, researchers focused on identifying genetic variations that can give rise to altered DNA methylation—a type of gene modification that can change the gene's expression without altering its DNA sequence. These genetic variations, called methylation quantitative trait loci (meQTLs), can thus indirectly affect the expression of one or more ASD risk genes.

Because previous research has shown that genetic variations associated with ASD can be identified using DNA from blood cells, these researchers looked for meQTLs in cord blood taken from infants at birth (who were later diagnosed with ASD) and in peripheral blood samples from 3- to 5-year old children with ASD. They also examined data from publicly available genetic maps of fetal brain tissue for meQTLs. Lung tissue meQTL data was used as a control because it was not likely to contain ASD-related variations.

The researchers mapped the meQTLs in all four types of tissues and looked for enrichment of known ASD-associated variations. They found enrichment of ASD-associated meQTLs in cord blood, peripheral blood, and brain tissue; importantly, this pattern was not observed in lung tissue. When looking at the ASD-associated meQTL targets, whose expression would be altered by the variation at the meQTL site, the researchers identified 37 different biological processes that would be affected. Of those, three were associated with methylation targets found in all three tissue types, 12 were found in brain tissue but not cord or peripheral blood, and 22 were found in both cord and peripheral blood but not brain tissue. Many of these processes are related to immune system function. This study expands on previous research, which indicates that differences in immune function are associated with ASD. Importantly, the authors of this study suggest that certain types of tissue can provide information about ASD-related immune system processes that may not be evident in the genotype.
QUESTION 3: WHAT CAUSES ASD, AND CAN DISABLING ASPECTS OF ASD BE PREVENTED OR PREEMPTED?

The results from this study provide further insight into the genetic variations that are associated with ASD, and the biological consequences of those variations. The fact that ASD-associated variations were apparent in blood samples is also significant because it suggests that future research need not rely solely on the use of brain tissue. Analyzed together, genetic and epigenetic data may provide a fuller and more accurate picture of the interactions among genes, biological factors, and ASD.
ASD is thought to be caused by a combination of genetic and environmental factors. Several behavioral and developmental problems that are common in ASD, such as intellectual, language, and attentional disabilities, are also common in individuals who have been exposed to toxic metals, such as lead, and in those with deficiencies in essential metals, such as zinc and manganese. To better understand potential environmental factors associated with ASD, the authors of this study examined whether toxic metal exposure and/or essential metal deficiencies play a role in the development of ASD.

To study these environmental factors while controlling for genetic variation, the researchers recruited discordant monozygotic (identical) and dizygotic (fraternal) twins — that is, pairs of identical and fraternal twins in whom one has ASD and the other did not — as well as sets of twins that both had ASD (concordant), and non-ASD twin controls. Seventeen pairs of identical twins and 15 pairs of fraternal twins participated in this study.

To study the exposure to toxic and essential metals before and after birth, the researchers examined the twins’ teeth, which provide a developmental record of metal exposure from the second trimester through early childhood stages. By collecting the twins’ lost deciduous teeth (those that naturally fall out during childhood) and analyzing them using mass spectrometry, the researchers were able to determine the concentrations of zinc, manganese, lead, and other metals at multiple developmental time points.

First, the researchers identified typical metal distribution patterns over the course of development by studying the teeth of non-ASD identical twins. They found that in typically developing children, manganese levels decline rapidly during the prenatal period and continue to decline after birth, while zinc levels remain steady during the prenatal period and then decline after birth. Next, they compared these patterns with those found in ASD-discordant identical and fraternal twins. They found that the affected twin’s manganese levels were lower both before and after birth, and zinc levels declined earlier during the prenatal period and increased to levels higher than the non-ASD twin’s after birth. In addition, they found higher levels of lead in the affected twin, particularly after birth. Further testing allowed the researchers to pinpoint the critical time period during which levels of these metals were the most different for the ASD-affected and non-ASD twin. These measurements indicated that lead levels were consistently higher in the ASD-affected twin between 10 and 20 postnatal weeks, while levels of tin in ASD-affected children were most different between 20 and 16 weeks before birth. Finally, ASD-affected children had the lowest levels of manganese – about 2.5 times less than the non-ASD twin – at postnatal week 15.
The researchers then compared the levels of zinc, manganese, and lead with the severity of ASD traits, as measured by scores on the Autism Diagnostic Observation Schedule Second Edition (ADOS-2) and Social Responsiveness Scale Second Edition (SRS-2). Though they found no significant association between zinc and measures of ASD severity or behavioral deficits, they found that low manganese levels were associated with higher scores on both the ADOS-2 and the SRS-2, and high lead levels were associated with higher ADOS-2 and SRS-2 scores.

The results of this study provide further evidence that environmental factors, particularly at prenatal and early postnatal developmental stages, may contribute to the development of ASD. However, the researchers note this study does not identify the causes of differences in the children's metal levels. Reduction in the levels of essential elements may not be due to lack of exposure but may instead be caused by biological dysregulation of essential metals, suggesting roles for both genetic and environmental factors in the development of ASD.
Prenatal exposure to fever is associated with autism spectrum disorder in the Boston Birth Cohort

Genetic and environmental factors are thought to contribute to ASD, and research suggests that prenatal exposure to maternal immune activation (MIA; a change in the prenatal environment when an immune response is activated in the mother) is associated with the development of ASD. However, the types of MIA exposure that are risk factors for ASD are not clearly defined. In this study, the researchers aimed to better understand the nature of maternal infections that increase the risk for ASD in U.S. minority populations that are underrepresented in the literature. They focused on MIA due to influenza, genitourinary tract infections, and fever in a population of predominantly low income, urban, minority mothers and subsequent ASD risk for their children.

For this study, the researchers used data from Boston-area mother-child pairs, including 116 children with ASD and 998 children without ASD. Mothers were interviewed 24-72 hours after giving birth and indicated whether they were exposed to a range of infections. The questionnaire also gathered information about covariates (additional variables that may affect the outcome of the study) such as the mother’s race, education level, marital status, and whether the mothers smoked prior to or during pregnancy. The mothers that had been exposed to either fever, genitourinary tract infections, or the flu provided further trimester-specific information about their exposures, and their babies underwent postnatal follow-ups to assess for ASD symptoms.

The researchers compared prenatal infection exposure and ASD risk both before and after accounting for covariates, and they found that no association exists between maternal genitourinary tract infections and risk of developing ASD or between prenatal flu exposure during any trimester and risk of developing ASD. The researchers did, however, identify a significant association between maternal fever at any point during pregnancy and risk for ASD. When broken down by trimester, the researchers additionally found an increased risk of ASD when the maternal fever occurred in the third trimester, but not the first or second.

These findings support and elaborate on past studies that suggest that MIA may increase the risk for ASD. They also note that existing literature does not agree on the role of anti-fever medication (such as acetaminophen) in later ASD diagnoses, meriting future research. The results of this study provide a basis for the development and improvement of clinical strategies to reduce the incidence of maternal fever and provide additional insight about the relationship between prenatal environment and ASD.
QUESTION 3: WHAT CAUSES ASD, AND CAN DISABLING ASPECTS OF ASD BE PREVENTED OR PREEMPTED?

**Maternal multivitamin intake, plasma folate and vitamin B\textsubscript{12} levels and autism spectrum disorder risk in offspring**


Since the discovery of its critical role in preventing neural tube defects during gestation, folate has become an essential supplement for women of reproductive age before and during pregnancy. Though studies show that individual folate levels vary from very low to higher than recommended, the average levels of plasma folate in pregnant women have increased 2.5 times as a result of increased supplementation with multivitamins and consumption of folate-fortified cereal grains. Conflicting findings in the literature make the association between increased maternal folate consumption and development of ASD unclear. Furthermore, vitamin B\textsubscript{12} is involved in many of the same biological pathways as folate, but there is limited research on its association with ASD risk. In this study, the researchers sought to clarify the association between increased risk of ASD development and multivitamin use, maternal plasma folate levels, and vitamin B\textsubscript{12} levels.

The participants of this study were 1,257 mother-child pairs who were recruited to the Boston Birth Cohort study. The researchers gathered information from the mothers 24-72 hours after birth about their multivitamin supplementation habits during pregnancy along with collecting maternal plasma folate and B\textsubscript{12} samples taken 2-3 days after birth and compared with ASD diagnostic information collected from their children’s electronic medical records. They found that during the first trimester, moderate multivitamin supplementation (three to five days per week) was associated with decreased risk of ASD – a finding that is consistent with the current literature. Moreover, both low supplementation (fewer than two times per week) and high supplementation (more than five times per week) were associated with an approximately 2.5 times increased risk of their child developing ASD. These results indicate that over- or under-utilization of multivitamins may both be associated with increased risk of ASD.

The researchers also measured maternal levels of plasma folate and vitamin B\textsubscript{12} at birth (which are good indicators of maternal levels during the third trimester of pregnancy) and found that very high folate levels (those in the top 10th percentile of the study population) were associated with increased risk of ASD, as were very high levels of B\textsubscript{12}. The risk was increased whether the mother had elevated levels of folate, B\textsubscript{12}, or both.

These findings present the possibility that too much or too little folate may be associated with an increased risk of ASD. The researchers present these findings with the hope that future research will clarify the relationship of plasma folate and B\textsubscript{12} levels with the development of ASD.
QUESTION 3: WHAT CAUSES ASD, AND CAN DISABLING ASPECTS OF ASD BE PREVENTED OR PREEMPTED?

Autism risk following antidepressant medication during pregnancy

When trying to understand the underlying causes of ASD, many researchers have considered the role of the medications taken by the mother during pregnancy and the risk of ASD. Results of previous studies investigating this issue have been equivocal. In this study, researchers sought to determine whether antidepressant use during pregnancy was associated with an increased risk of ASD.

The researchers followed a population-based Swedish cohort of 179,007 children from birth (in 2006-2007) until age 7 or 8 (in 2014). They used clinical diagnoses obtained from the Swedish Patient Register to determine whether the children had been diagnosed with ASD, and whether either parent had at least one psychiatric diagnosis listed. They also used the Swedish Prescription Drug Register to determine whether the mothers had been prescribed antidepressant medication during pregnancy, as evidence of child exposure to antidepressants. Based on these data, 13.2% of the parents in the study had a diagnosed mental illness; 0.9% of the children had an ASD, and among those, 61% were diagnosed with autistic disorder.

The researchers then measured the relative risk of ASD in the children who had been exposed to antidepressant medications during gestation. To minimize the possibility of including children of mothers who stopped taking antidepressants during pregnancy in the exposed group, children were classified as exposed only if their mothers had filled their antidepressant prescription on at least two occasions that overlapped with their pregnancies. The researchers found a 1.3 times increased relative risk of having ASD in the children of mothers that had taken any antidepressant during pregnancy. This risk was reduced to 1.07 after accounting for confounding variables, such as whether the mother had received a psychiatric diagnosis in her lifetime. When determining the risk associated with exposure to individual antidepressant medications in the subset of women diagnosed with a psychiatric disorder, they found that the greatest increased risks were for citalopram and escitalopram (1.47 times) and clomipramine (2.86 times). After controlling for other variables however, the relative risks calculated by the authors throughout the study were reduced to near-negligible levels.

The findings of this study do not indicate that maternal antidepressant use can increase the risk of ASD. Rather, the authors proposed that confounding variables contributed to the relative risks demonstrated. Specifically, ASD and other psychiatric disorders may be caused by similar underlying genetic factors. Thus, the presence of a gene variant that contributes to maternal depression could increase the risk of her child developing ASD, which may confound this and other studies investigating the link between antidepressant use and ASD risk. In addition, although these findings may have implications for clinician recommendations about medication use during pregnancy, untreated mental health conditions are themselves associated with poor health outcomes. Thus, the researchers do not believe these findings support the discontinuation of antidepressant use during pregnancy.
There are conflicting reports in the literature regarding the association between folic acid supplementation during a mother's pregnancy and risk for developing ASD in her child. The purpose of this article was to review the current literature on this topic and provide clarification of the nature of this association.

The researchers conducted a meta-analysis, i.e., they combined and re-analyzed data from 16 studies with a total of 4,514 participants with ASD. They excluded any articles that did not present data specific to the relationship between folic acid supplementation during pregnancy and ASD, and articles that did not offer sufficient human subjects data were not considered eligible. Overall, the researchers found that folic acid supplementation during pregnancy was significantly associated with a decreased risk of developing ASD compared to those without folic acid supplementation. They considered whether there were variations in ASD risk based on study type or race and found that the results were consistent across different study types and for Asian, European, and American populations.

Although the researchers identified high heterogeneity (variation in study outcomes) between studies when all the data were pooled, they found no evidence that it was attributable to differences in when, where, or how these studies were conducted. The researchers suggest that the variation may be due instead to unmeasured genetic or environmental factors, which may act as confounding variables. Furthermore, sensitivity analysis showed that no single study had excessive influence on the pooled result while excluding one study at a time. Although it is possible that the mothers may not have accurately remembered their folic acid intake years after pregnancy, future studies can account for this potential recall bias by ensuring that data is collected from mothers who were recently pregnant.

Though this study provides strong evidence to suggest that folic acid supplementation decreases the risk of ASD, the researchers concluded that future studies should address questions such as the timing or dosage of folic acid supplementation during pregnancy.
ASD is associated with impairments in adaptive behaviors, including social, communication, and independent living skills. Several assessment instruments exist for measuring these impairments, including the Vineland Adaptive Behavior Scales, Second Edition (Vineland-II). These tools are used to assess the extent of social and behavioral impairments such as communication, daily living skills, socialization, and motor skills. They can also be used to track progress over time, including during and after an intervention. A change in the Vineland-II score may indicate a meaningful benefit in daily life, but other factors such as age or cognitive ability may affect the effectiveness of an intervention. More importantly, it is not yet clear what amount of change in assessment score on the Vineland-II is clinically significant. Therefore, the researchers in this study sought to determine the smallest score change on the Vineland-II that could be considered clinically meaningful (known as the Minimal Clinically Important Difference, or MCID) and investigate if MCID could be dependent on other clinical factors.

The researchers used existing datasets to compare data from over 9,000 individuals with ASD who had been assessed with the Vineland-II. They used two types of analysis to determine the Vineland-II MCID: 1) a distribution-based MCID estimate, to calculate the amount of change not due to normal variation and 2) an anchor-based MCID estimate, to “anchor” an amount of change to other assessment scales in which clinically meaningfulness has already been established.

Subject data was grouped based on age (0 to less than 13 years, 13 to less than 18 years, and 18+ years) and by IQ (IQ less than 70, IQ 70 or greater). Across all groups, the MCID estimated score change by the anchor-based method ranged from 2.44 to 3.76, and by the distribution-based estimate ranged from 2.01 to 3.20. Lower estimates were seen among younger populations and those with lower IQ scores. The researchers also compared differences in MCID values based on sex and saw no significant difference between males and females. Overall, these results indicate that a score change on the Vineland-II between 2.00 and 3.75 points reflects clinically meaningful change for individuals with ASD across all age groups, IQ levels, and sexes. The results of this study are important because they establish a score change value that will help clinicians better understand the effectiveness of a treatment or intervention.
A randomized, placebo-controlled trial of metformin for the treatment of overweight induced by antipsychotic medication in young people with autism spectrum disorder: open-label extension


Children with ASD who display disruptive behaviors are often treated with atypical antipsychotic medications, for which a common side effect is significant weight gain. Because atypical antipsychotic medications can be highly effective at decreasing disruptive behaviors, clinicians sometimes suggest that continuing the medication while treating the negative side effects is preferable to discontinuing the medication altogether.

Metformin is a drug that can treat weight gain through increased insulin sensitivity, meaning the body will absorb and produce less glucose (sugar). In this study, researchers tested the effectiveness of metformin for managing weight gain in children who take antipsychotics for ASD-related disruptive behaviors. In the first phase of the study, children with ASD aged 6 to 17 years-old who reported weight gain while taking antipsychotic drugs were given either metformin or a placebo for 16 weeks. In the second phase, the children who were previously given metformin in the first phase continued taking it for another 16 weeks (M-M group), and the children who were previously given a placebo began taking metformin for 16 weeks (P-M group). The researchers wanted to know if 1) children in the M-M group were able to maintain their weight loss from the initial phase of the trial, and 2) children in the P-M group would begin to lose weight when they switched from the placebo to metformin. The researchers used weight and body mass index (BMI) to measure the effectiveness of metformin.

In the first phase of the trial, the average weight and BMI for the children in the M-M group was significantly reduced, while that of the P-M group did not change. In the second phase of the trial, the average weight and BMI of the M-M group was unchanged relative to the end of phase I, while that of the P-M group was significantly reduced. These results indicate that metformin is effective in reducing weight and maintaining weight loss in children who experience weight gain as a side effect of atypical antipsychotic medications. Therefore, use of metformin may be an effective management approach for controlling weight gain. Although the researchers noted that the group who started metformin experienced a four- to eight-week delay before weight reduction became apparent, longer-term outcomes indicate that children with ASD continue to benefit from use of an atypical antipsychotic medication.
Parent-delivered early intervention in infants at risk for ASD: effects on electrophysiological and habituation measures of social attention


Research suggests that children with ASD may have impairments in social attention that can be measured through brain activity detectable before behavioral signs arise. Early detection and diagnosis of ASD is important because early intervention can improve social attention and other outcomes. Importantly, research suggests that interventions administered by parents can increase parental responsiveness to infants’ communication cues. Furthermore, these at-home interventions may be beneficial for at-risk populations, particularly for infants with developmental disabilities and for families who live in low-resource communities. In this study, researchers tested a parent-mediated intervention designed to promote parent-infant interaction with the goal of proactively stimulating brain activity important to social attention. Infants at age 6 months were identified as either high-risk (the infant had an older sibling with ASD) or low-risk. Infants in the high-risk groups were randomized to receive either assessment and monitoring only, or a promoting first relationships (PFR) intervention administered between age 9 months and 11 months. The PFR intervention involved a trained mental health professional who met with the caregiver and their infant approximately 1 hour per week for 10 weeks and focused on promoting caregiver-infant interaction and infant social development.

Researchers assessed the social attention of the infants at 6 (baseline), 12 (endpoint), and 18-months (follow-up). At each time point, the researchers measured the children’s 1) habituation to (time spent looking at) faces and objects, 2) brain activity in response to social and non-social videos, and 3) brain activity in response to faces and objects. Brain activity was measured using electroencephalographic (EEG) recordings of electrical activity in the brain. They predicted that the children who participated in the PFR intervention would show decreased habituation time to faces (indicating that the children learned to more quickly encode and recall a novel face), increased brain activity in response to social videos, and increased brain activity in response to faces rather than objects.

The researchers found that children who received the PFR intervention showed decreased habituation time to faces over both time periods, indicating an improvement in learning and information processing. This effect was not seen in the children who did not participate in the PFR intervention. Additionally, the children who participated in the PFR intervention showed increased brain activity in response to both social and non-social videos, as compared to the children in the non-intervention group. Finally, children who participated in the PFR intervention showed larger and more prolonged neural responses to faces than to objects, indicating more in-depth processing of social cues. The children who did not participate in the intervention showed larger and more prolonged responses to objects than to faces.

These findings suggest that initiating interventions prior to the onset of symptoms in high-familial risk children may reduce early signs of ASD symptoms and cascading effects of having difficulty in processing social cues. As high-familial risk children have about a 20% chance of developing ASD, these interventions might be valuable to improving outcomes in these children.
QUESTION 5

WHAT KINDS OF SERVICES AND SUPPORTS ARE NEEDED TO MAXIMIZE QUALITY OF LIFE FOR PEOPLE ON THE AUTISM SPECTRUM?

Though children and adults with ASD often require significant support from healthcare systems, commercial insurers have historically provided little coverage of ASD assessment and treatment. As of spring 2018, forty-six states and the District of Columbia have enacted autism insurance mandate legislation, which require commercial insurance plans to pay for services for children with ASD. The goal of this study, which was conducted when only 29 states had enacted mandates, was to determine whether those insurance mandates resulted in increased use and spending for healthcare services among children with ASD.

The researchers used insurance claims data from three major insurance companies from 2008 to 2012 for children 21 years and younger with ASD. They compared monthly healthcare service use and spending by children who were eligible for insurance mandates to children who were not eligible for insurance mandates. Specifically, they compared service use and spending across four overlapping categories: 1) all health care services, 2) all services associated with an ASD diagnosis, 3) outpatient services associated with an ASD diagnosis, and 4) outpatient behavioral and functional therapy associated with an ASD diagnosis.

The researchers found that children who were covered by insurance mandates were 3.4 percentage points more likely to use ASD-specific services and spent an average of $77 more per month on ASD-specific services than children who were not covered. This increase was more substantial for younger children (ages 0-5) than for older children (6-12); there was no significant increase among children ages 13-21. Insurance mandates were associated

Effects of state insurance mandates on health care use and spending for autism spectrum disorder
Question 5: What kinds of services and supports are needed to maximize quality of life for people on the autism spectrum?

With increased spending across all health care services and mostly accounted for by outpatient services. Spending increases were also affected by the number of years that passed since the insurance mandate was enacted, with a continual rise in spending from the first year after implementation to the third year.

The researchers suggest that the larger spending increases for younger children are because community providers are better equipped to provide ASD intervention for younger children than for older children. Additionally, as children get older, ASD-specific services tend to be paid for by the educational system instead of the healthcare system. The difference between service use in younger versus older children also could be because many insurance mandate laws apply only to younger children. The results also suggest that there is a time delay between the enactment of a mandate and its full impact on health care spending, due in part to the amount of time needed to establish regulatory and reimbursement processes.

Overall, the results of this study indicate that state-imposed health insurance mandates increase the use of healthcare services by children and adolescents with ASD and may therefore be an effective way to increase access to treatment.
Early intervention programs can improve long-term outcomes in children with ASD. Because of the costs associated with such interventions is very high, it is important to demonstrate long-term cost-effectiveness. Few studies have directly measured long-term cost-effectiveness, with most having used cost simulations. This study directly estimates the cost-effectiveness of the Early Start Denver Model (ESDM), an early intervention program for children 12-60 months of age. The ESDM program uses applied behavior analysis (ABA) approaches and has been shown to improve cognition, language skills, social abilities, and adaptive behavior in children with ASD. The researchers wanted to determine whether participation in the ESDM program reduced health- and intervention-related costs after the intervention was over.

The researchers used data from a randomized controlled trial of 39 children aged 18-30 months with ASD. Twenty-one of these children participated in the ESDM program and 18 received community-based treatment. The data included what health-related services were used by each child during the intervention until children were 6 years old. The researchers compared the average cost of services between the intervention and control groups during the intervention period and then after the intervention ended. They estimated average costs and time spent for different services, including ABA, early intensive behavior intervention (EIBI), and speech therapy services based on the typical costs of these services.

During the intervention period, the average costs for children in the ESDM program was approximately $14,000 higher than the children in the community-based treatment program; this difference was not statistically significant. During the intervention period, children in the ESDM group spent fewer hours using ABA, EIBI, and speech therapy services than children in the community-based intervention group. The decreased utilization of these services partially off-set the higher cost of the ESDM program.

In the post-intervention period, children in the ESDM group received significantly fewer hours of ABA, EIBI, and speech therapy services than the community-based treatment group. This translated into significantly lower costs for children who had participated in the ESDM program, (approximately $19,000 lower annually) than for children who had participated in the community-based treatment program. This result was statistically significant.

In summary, the researchers conclude that the initial cost associated with the ESDM program was entirely offset in the post-intervention period. Children that received the ESDM required fewer services in the years following intervention and thereby lowered health-related costs overall.
Research suggests that individuals with ASD are at higher risk of early death than the general population. Previous studies have suggested that this increased risk may be associated with intentional and unintentional injuries, however these studies have been limited by population size and location. The goal of this study was to examine the causes of death in a large population of individuals with ASD in the U.S. who died between 1999 and 2014.

The researchers reviewed death records in the National Vital Statistics System, a database that contains information about causes of death and demographics. In the time frame of the study, there were 1,367 recorded deaths of individuals with diagnosed ASD (1,043 males and 324 females). The average age at death of these individuals was 36.2 years, as compared to an average age at death of 72 years across the general population.

Although previous studies have examined the relationship between premature mortality and ASD, few have focused on injury as a contributor to the high mortality rate among those with ASD. In this study, the researchers discovered that individuals with ASD were three times more likely than the general population to have died due to an unintentional injury. Overall, unintentional injury accounted for 27% of recorded deaths. Suffocation, asphyxiation, and drowning accounted for 79.4% of all injury-related death in children with ASD, and children younger than 15 years old were at elevated risk.

There may still be a significant underreporting of ASD-related deaths, especially deaths from unintentional injury. Therefore, these results present a public health concern and the researchers propose the development and implementation of prevention approaches, such as swimming lessons, to decrease these risks in individuals with ASD, particularly those who are younger than 15 years old.
QUESTION 7

HOW DO WE CONTINUE TO BUILD, EXPAND, AND ENHANCE THE INFRASTRUCTURE SYSTEM TO MEET THE NEEDS OF THE ASD COMMUNITY?

Autism spectrum disorder among US children (2002-2010): socioeconomic, racial, and ethnic disparities

Evidence suggests that there are socioeconomic and racial disparities in the prevalence of ASD in the United States. The researchers previously found that ASD tends to be more prevalent among non-Hispanic White children than either non-Hispanic Black children or Hispanic children, as well as among children from families with higher socioeconomic status (SES). Since their earlier study, the overall prevalence of ASD in the US has more than doubled from 6.6 per 1,000 in 2002 to 14.7 per 1,000 in 2010. Here, the researchers aimed to determine whether the socioeconomic, racial, and ethnic differences that they had previously observed were persistent as overall prevalence increased.

The researchers pulled data from the Centers for Disease Control and Prevention’s Autism and Developmental Disabilities Monitoring (ADDMD) Network across the years 2002 to 2010. They used data from 11 states: Alabama, Arizona, Arkansas, Colorado, Georgia, Maryland, Missouri, New Jersey, North Carolina, Utah, and Wisconsin. They selected household education level as their primary measure of SES and defined three SES groups (low, middle, and high).

Across all three SES groups, ASD prevalence increased steadily over the time period surveyed, and prevalence was lowest in the low SES group and highest in the high SES group. The difference in ASD prevalence between high- and low-SES children did not change from 2002 to 2010.
QUESTION 7: HOW DO WE CONTINUE TO BUILD, EXPAND, AND ENHANCE THE INFRASTRUCTURE SYSTEM TO MEET THE NEEDS OF THE ASD COMMUNITY?

When comparing ASD prevalence across racial and ethnic backgrounds, they found that prevalence is higher in non-Hispanic White children than non-Hispanic Black or Hispanic children. This difference is greater for children in low SES communities.

Importantly, the researchers suggest that high SES or non-Hispanic White ethnic background are most likely not risk factors for ASD. Rather, the more likely reason for these disparities is care bias: high SES and non-Hispanic White children have greater access to healthcare services for the diagnosis and treatment of ASD and are therefore more highly represented in prevalence estimates.
What is the male-to-female ratio in autism spectrum disorder? A systematic review and meta-analysis

ASD is more commonly diagnosed in boys than in girls. Though the DSM-5 states that the male-to-female ratio of ASD prevalence is 4:1, various studies suggest that the true ratio could range from 2:1 to 8:1. In order to obtain a more accurate male-to-female prevalence estimate, researchers performed a meta-analysis to examine data from 54 studies that independently examined this question. The researchers limited their analysis to studies of children with ASD from 0-18 years of age and studies with a sample size of at least 1,500 children.

For each study, the researchers calculated the male-to-female odds ratio (MFOR), a measure of the odds of being male in the group of subjects with ASD compared with the odds of being male in the non-ASD group. This metric is interchangeable with the male-to-female ratio and allows the researchers to control for the overall male-to-female ratio in non-ASD individuals.

As expected, the researchers found a large degree of variability between the studies. They used measures of study quality and study methodology to determine which results should weigh more heavily in their estimate of the MFOR. Based on their assessment of study quality, they estimated a higher number of females with ASD than the current consensus and concluded that the male-to-female ratio is ASD prevalence is between 3:1 and 3.5:1.

To reduce gender bias in diagnosing ASD, it is important to consider that the prevalence of ASD is higher in females than previous reports have indicated. Studies suggest that ASD diagnosis is more difficult in girls, who often have learned to mask their difficulties and whose ASD traits tend to be less overt in general. Importantly, the diagnostic criteria are based on male presentation of ASD, and girls with ASD are more likely to be overlooked, misdiagnosed, or identified late. The researchers note that their results do not counter the evidence that boys are more vulnerable to ASD than girls.
ARTICLES SELECTED FOR THE 2017 SUMMARY OF ADVANCES

QUESTION 1: HOW CAN I RECOGNIZE THE SIGNS OF ASD, AND WHY IS EARLY DETECTION SO IMPORTANT?


QUESTION 2: WHAT IS THE BIOLOGY UNDERLYING ASD?


QUESTION 3: WHAT CAUSES ASD, AND CAN DISABLING ASPECTS OF ASD BE PREVENTED OR PREEMPTED?


QUESTION 4: WHICH TREATMENTS AND INTERVENTIONS WILL HELP?


QUESTION 5: WHAT KINDS OF SERVICES AND SUPPORTS ARE NEEDED TO MAXIMIZE QUALITY OF LIFE FOR PEOPLE ON THE AUTISM SPECTRUM?


QUESTION 6: HOW CAN WE MEET THE NEEDS OF PEOPLE WITH ASD AS THEY PROGRESS INTO AND THROUGH ADULTHOOD?


QUESTION 7: HOW DO WE CONTINUE TO BUILD, EXPAND, AND ENHANCE THE INFRASTRUCTURE SYSTEM TO MEET THE NEEDS OF THE ASD COMMUNITY?


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QUESTION 7: HOW DO WE CONTINUE TO BUILD, EXPAND, AND ENHANCE THE INFRASTRUCTURE SYSTEM TO MEET THE NEEDS OF THE ASD COMMUNITY?


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