SEED: Study to Explore Early Development

Researchers working on the Study to Explore Early Development (SEED) have recently published many studies reporting on important findings related to autism spectrum disorder (ASD). These studies used data collected from the first phase of SEED (SEED 1). The scientific findings for all SEED studies published to date are summarized below.

Many additional studies are underway. We will provide summaries of those studies in the future.

Reports Outlining SEED Methods and Descriptions of the SEED Study Sample

SEED investigators have prepared several reports detailing the study methods and describing the children enrolled in the SEED sample. These reports provide foundational information about SEED for other researchers, policymakers, and clinicians.

The Study to Explore Early Development (SEED): a multisite epidemiologic study of autism by the Centers for Autism and Developmental Disabilities Research and Epidemiology (CADDRE) network.

Schendel DE, Diguiseppi C, Croen LA, Fallin MD, Reed PL, Schieve LA, Wiggins LD, Daniels J, Grether J, Levy SE, Miller L, Newschaffer C, Pinto-Martin J, Robinson C, Windham GC, Alexander A, Aylsworth AS, Bernal P, Bonner JD, Blaskey L, Bradley C, Collins J, Ferretti CJ, Farzadegan H, Giarelli E, Harvey M, Hepburn S, Herr M, Kaparich K, Landa R, Lee LC, Levenseller B, Meyerer S, Rahbar MH, Ratchford A, Reynolds A, Rosenberg S, Rusyniak J, Shapira SK, Smith K, Souders M, Thompson PA, Young L, Yeargin-Allsopp M.

Journal of Autism and Developmental Disorders, 2012

This report describes SEED methods. SEED is one of the largest studies investigating genetic and environmental risk factors for autism spectrum disorder (ASD) and child health and behavioral traits associated with ASD. SEED enrolls preschool-aged children with ASD and other developmental disabilities and children from the general population in six sites across the United States. SEED methods focus on enrolling families from diverse populations in each area. A key strength of SEED includes the collection of in-depth information on child development, which allows researchers to more rigorously classify children into various study groups (ASD, other developmental disabilities, or population controls) than what is done in many other ASD research studies. In SEED, researchers use standardized assessment tools to determine a children's final study group and to assess specific behavioral traits among children with ASD. Another key strength is the collection of comprehensive data on child health and potential risk factors for ASD. SEED's large and diverse sample of study participants allows researchers to analyze data in greater detail than most other ASD studies and answer many important questions about ASD.

Using standardized diagnostic instruments to classify children with autism in the Study to Explore Early Development.

Wiggins LD, Reynolds A, Rice CE, Moody EJ, Bernal P, Blaskey L, Rosenberg SA, Lee LC, Levy SE.

Journal of Autism and Developmental Disorders, 2015

This report describes the SEED process for determining whether a child enrolled in the study will be classified as an ASD case. This classification is based on an in-person assessment given by trained SEED clinicians. Children enrolled in the study are screened for autism symptoms by asking their mothers to respond to a brief questionnaire. Children with an indication of possible autism symptoms are assessed further during an in person visit. Clinicians give these children a more in-depth developmental evaluation known as Autism Diagnostic Observation Schedule and ask their mothers or other caregivers to participate in an interview known as the Autism Diagnostic Interview – Revised. Besides providing clinicians with information to determine a child's ASD classification, these assessments provide valuable information on ASD-specific behaviors and traits, allowing researchers to better understand the different characteristics among children with ASD.

Brief Report: The ADOS Calibrated Severity Score Best Measures Autism Diagnostic Symptom Severity in Pre-School Children.

Wiggins LD, Barger B, Moody E, Soke GN, Pandey J, Levy S.

Journal of Autism and Developmental Disorders, 2017

This report describes SEED methodology for assessing autism symptom severity among children with ASD. Measuring a child's autism symptoms is often challenging because many children with ASD also have other developmental conditions. This can make it difficult to separate a child's social and communication challenges from the child's other developmental delays or conditions. Researchers evaluated several measures of autism severity and found that the Autism Diagnostic Observation Schedule (ADOS) calibrated severity score best measured the severity of core autism symptoms in a way that did not include symptoms of other developmental conditions. Because of findings from this study, the ADOS calibrated severity score will be used in other SEED research to help scientists better understand how the severity of autism symptoms relates to ASD risk factors and health outcomes.

More Information:
To learn more about ASD, please visit: **www.cdc.gov/autism**
To learn more about SEED, please visit: **www.cdc.gov/SEED**

Demographic Profile of Families and Children in the Study to Explore Early Development (SEED): Case-control Study of Autism Spectrum Disorder.

DiGuiseppi CG, Daniels JL, Fallin MD, Rosenberg SA, Schieve LA, Thomas KC, Windham GC, Goss CW, Soke GN, Currie DW, Singer AB, Lee LC, Bernal P, Croen LA, Miller LA, Pinto-Martin JA, Young LM, Schendel DE.

Disability and Health Journal, 2016

This is one of two reports that describe the characteristics of children enrolled in SEED. This report focuses on sociodemographic characteristics. SEED successfully enrolled a highly diverse sample of participants, including minorities and low socioeconomic status families. The SEED population sample represents racial, ethnic, and demographic diversity in the United States. SEED improves upon other ASD risk factor studies in that it does not rely on administrative data sources, which lack many important details of both child development and maternal risk factors. Nor does it rely on small samples from only a few clinics or schools. SEED collects detailed data in a large and diverse sample. This provides unique opportunities for researchers to learn more about how socioeconomic characteristics relate to risk factors for ASD and health outcomes in children with ASD.

Autism Spectrum Disorder Symptoms among Children Enrolled in the Study to Explore Early Development (SEED).

Wiggins LD, Levy SE, Daniels J, Schieve L, Croen LA, DiGuiseppi C, Blaskey L, Giarelli E, Lee LC, Pinto-Martin J, Reynolds A, Rice C, Rosenberg CR, Thompson P, Yeargin-Allsopp M, Young L, Schendel D.

Journal of Autism and Developmental Disorders, 2015

This is one of two reports that describe the characteristics of children enrolled in SEED. This report focuses on developmental characteristics. Children enrolled in SEED are divided into four groups: three with children who have varying types of developmental delays and disabilities, including ASD, and one with children from the general population. The report describes how various facets of children's development vary across these four groups and highlights the many needs of children with ASD and other developmental disabilities.

SEED Studies of ASD Risk Factors

Maternal and Paternal Infertility Disorders and Treatments and Autism Spectrum Disorder: Findings from the Study to Explore Early Development.

Schieve LA, Drews-Botsch C, Harris S, Newschaffer C, Daniels J, DiGuiseppi C, Croen LA, Windham GC.

Journal of Autism and Developmental Disorders, 2017

This study examined associations between ASD and whether, prior to becoming pregnant, a child's mother had a condition that might have affected her ability to get pregnant (i.e., infertility). The study also looked at whether the mother had received any medical treatments to help her become pregnant or to prevent miscarriage during early pregnancy. SEED's detailed data on specific types of infertility disorders and treatments allowed researchers to conduct a much more in depth analysis on this topic than those that have been done previously. The study findings show that several infertility disorders in the mother -- including blocked tubes, uterine conditions such as fibroids, endometriosis, and polycystic ovarian syndrome -- are associated with ASD in children. However, treatments for infertility or to prevent miscarriage were not associated with ASD. While the reasons for the associations with infertility conditions could not be studied, possible explanations include increased inflammation during pregnancy or problems with the mother's immune system. The findings from this study add to studies of other risk factors highlighting the relationship between maternal health before and during pregnancy and ASD.

Prenatal Alcohol Exposure in Relation to Autism Spectrum Disorder: Findings from the Study to Explore Early Development (SEED).

Singer AB, Aylsworth AS, Cordero C, Croen LA, DiGuiseppi C, Fallin MD, Herring AH, Hooper SR, Pretzel RE, Schieve LA, Windham GC, Daniels JL.

Paediatric and Perinatal Epidemiology, 2017

This study examined associations between alcohol use just before and during pregnancy and ASD or other developmental disabilities (DDs). Previous studies have shown that high levels of alcohol use in pregnancy are associated with child developmental effects, such as decreased intellectual ability, hyperactivity, learning difficulties, and autism-like traits. This study investigated whether lower levels of alcohol use before and during pregnancy were associated with developmental outcomes. Most mothers of children in SEED reported no or low levels of alcohol use before or during their pregnancies. In fact, nearly all mothers reported no alcohol use in the second month of pregnancy or later (93-98% depending on month). Therefore, a main focus of the study was on alcohol use in the three months prior to pregnancy or the first month of pregnancy. The study findings show that modest alcohol use during these four months was not associated with increased risk for either ASD or other DDs. Although this study did not find an association between ASD or other DDs and modest alcohol use before or during pregnancy, women who are pregnant or planning to become pregnant should continue to follow recommendations to avoid alcohol use because of other known effects on infant and child health.

Autism Spectrum Disorder and Birth Spacing: Findings from the Study to Explore Early Development (SEED).

Schieve LA, Tian LH, Drews-Botsch C, Windham GC, Newschaffer C, Daniels JL, Lee LC, Croen LA, Fallin MD.

Autism Research, 2017

This study examined whether the amount of time between pregnancies was associated with ASD or other developmental disabilities in children. SEED's detailed data on ASD subgroups and other developmental disabilities allowed researchers to conduct a more in depth analysis on this topic than those that have been done previously. The study findings show that both shorter and longer time periods between births are associated with having a child with ASD. Children conceived less than 18 months after their mother's previous birth and children conceived 60 or more months after their mother's previous birth were more likely to have ASD than children conceived between 18 to 59 months after their mother's previous birth. The relationship was stronger in children with more severe ASD symptoms. Also, the association between birth spacing and ASD appeared to be unique to ASD, as there was no association found between birth spacing and having children with other developmental disabilities. The association between birth spacing and ASD was not explained by unplanned pregnancy, an underlying fertility disorder in the mother, or high blood pressure or diabetes during pregnancy. The findings from this study can help healthcare providers counsel their patients on pregnancy spacing.

Maternal Exposure to Occupational Asthmagens During Pregnancy and Autism Spectrum Disorder in the Study to Explore Early Development.

Singer AB, Windham GC, Croen LA, Daniels JL, Lee BK, Qian Y, Schendel DE, Fallin MD, Burstyn I.

Journal of Autism and Developmental Disorders, 2016

This study examined whether ASD was associated with the mother's workplace exposure to certain chemicals or other substances during pregnancy. Because previous studies have shown associations between maternal asthma and allergy and ASD, researchers were particularly interested in exposure to substances that are known to trigger asthma symptoms, called asthmagens. Examples of asthmagens include latex, certain drugs and chemicals such as dyes, and some cleaning products. The findings show that mothers of children with ASD had been exposed to slightly higher levels of workplace asthmagens than mothers of children in the general population. However, the difference was small and could have been due to chance. Many gaps remain in our understanding of how environmental exposures might impact the risk for ASD, and further research is needed.

Associations Between the 2nd to 4th Digit Ratio and Autism Spectrum Disorder in Population-Based Samples of Boys and Girls: Findings from the Study to Explore Early Development.

Schieve LA, Tian L, Dowling N, Croen L, Hoover-Fong J, Alexander A, Shapira SK.

Journal of Autism and Developmental Disorders, 2018

This study examined associations between ASD and the ratio of children's index (2nd) finger length to their ring (4th) finger length. The ratio of finger lengths (or digit ratio) has been linked to the level of sex hormones a child was previously exposed to during pregnancy. Researchers study digit ratios because they rarely have direct measurements of fetal exposure to hormones. Study findings in boys showed that digit ratio was associated with ASD, but only in certain subgroups, such as children who had ASD and also a birth defect or genetic syndrome. This suggests the association might not have been related to hormone levels, but might instead be explained by genetics. Study findings in girls showed that digit ratio was associated with ASD and that the association was not limited to certain subgroups of children. There has been little past study of the association between digit ratio and ASD, particularly in girls. The findings in this report suggest that hormone exposures during pregnancy might be related to ASD in girls, but many gaps remain in our understanding of the underlying reasons for this association and further research is needed.

SEED Studies of Risk Factors Associated with Adverse Child Outcomes More Generally

Presence of an Epigenetic Signature of Prenatal Cigarette Smoke Exposure in Childhood.

Ladd-Acosta C, Shu C, Lee BK, Gidaya N, Singer A, Schieve LA, Schendel DE, Jones N, Daniels JL, Windham GC, Newschaffer CJ, Croen LA, Feinberg AP, Fallin MD.

Environmental Research, 2016

This study examined how environmental exposures, such as smoking during pregnancy, may impact gene regulation in children. Gene regulation is the process by which genes in a cell are turned on or off, and it is important for child development. Like other studies, researchers found that smoking during pregnancy affected gene regulation in children. However, while other studies have assessed these effects in children at the time of birth, the SEED sample provided an opportunity to look at gene regulation in older children. This study showed that the same pattern of gene effects was present in older children whose mothers had smoked in pregnancy as had been previously observed in newborns. These findings suggest that the gene marks in older children may reflect their mothers' smoking during pregnancy.

SEED Studies of the Characteristics and Health and Well-being of Children with ASD and other Developmental Disabilities

Injuries in Children with Autism Spectrum Disorder: Study to Explore Early Development (SEED).

DiGuiseppi C, Levy SE, Sabourin KR, Soke GN, Rosenberg S, Lee LC, Moody E, Schieve LA.

Journal of Autism and Developmental Disorders, 2017

This study evaluated injuries in preschool-aged children with and without ASD and other developmental disabilities (DDs). Parents of children were asked whether their child had ever had an injury that required medical attention, and what types of injuries had occurred. The study findings showed that injuries were common in all groups of children and there was little difference between groups. Parents reported injuries for 32% of children with ASD, 28% of children with other DDs, and 30% of children in the general population. The most common injuries were open wounds and fractures and the most common reason for injuries was falls. While there was a slight difference in injuries between children with ASD and other DDs, further study found that this was largely explained by a higher level of attention problems in the children with ASD.

Self-injurious Behaviors in Children with Autism Spectrum Disorder Enrolled in the Study to Explore Early Development.

Soke GN, Rosenberg SA, Rosenberg CR, Vasa RA, Lee LC, DiGuiseppi C.

Autism, 2017

This study assessed self-injurious behavior, or SIB, among children with ASD. SIB includes head-banging, hair-pulling, arm-biting, scratching, and hitting oneself. SIB is usually mild, but can be severe in some children and may result in injuries requiring medical care. Children with severe SIB may miss out on educational and social activities. This study showed that in the SEED sample, about 28% of preschool-aged children with ASD displayed SIB currently, and 47% had previously displayed SIB. Researchers found SIB was more common in children with low adaptive behavior scores and gastrointestinal, sleep, and behavioral problems. While its causes are not completely understood, identifying SIB early is helpful because it may reduce the likelihood of more severe SIB later.

Brief Report: Self-Injurious Behaviors in Preschool Children with Autism Spectrum Disorder Compared to Other Developmental Delays and Disorders.

Soke GN, Rosenberg SA, Rosenberg CR, Vasa RA, Lee LC, DiGuiseppi C.

Journal of Autism and Developmental Disorders, 2018

This study assessed self-injurious behavior, or SIB, among preschool-aged children with ASD in comparison to children with other developmental disabilities (DDs). The study showed that SIB is common in two groups of preschool-aged children – those with ASD and those for whom some autism-related symptoms are reported by their mother or other caregiver, even though they didn't meet the criteria to be classified as an ASD case. SIB was much less common in children with other DDs whose mother or caregiver did not report autism-related symptoms. These findings suggest that clinicians working with young children with DDs consider screening for SIB, even in children who do not have an ASD diagnosis.

Homogeneous Subgroups of Young Children with Autism Improve Phenotypic Characterization in the Study to Explore Early Development.

Wiggins LD, Tian LH, Levy SE, Rice C, Lee LC, Schieve L, Pandey J, Daniels J, Blaskey L, Hepburn S, Landa R, Edmondson-Pretzel R, Thompson W.

Journal of Autism and Developmental Disorders, 2017

This study used a complex computer program to assess the wide range of developmental characteristics among children with ASD. Researchers identified four subgroups of children within the ASD group: 1) children with mild language delay and average cognitive functioning, but increased cognitive rigidity (or difficulty changing behaviors); 2) children with significant developmental delay, below average cognitive functioning, and repetitive motor behaviors; 3) children with general developmental delay, below average cognitive functioning, and moderate to highly severe autism symptoms; and 4) children with mild language and motor delays, but increased cognitive rigidity and high rates of problem behaviors. This study shows how information on developmental characteristics can be studied using advanced statistical methods to better understand ASD. This information might also be useful in understanding children's future health and development.

The Prevalence of Gluten Free Diet Use among Preschool Children with Autism Spectrum Disorder.

Rubenstein E, Schieve L, Bradley C, DiGuiseppi C, Moody E, Thomas K, Daniels J.

Autism Research, 2017

This study estimated the proportion of children with ASD who had been on a gluten free diet. Altogether, 20% of preschool-aged children with ASD were currently or previously using a gluten free diet. In contrast, only 1% of children in the general population control group were using a gluten free diet. Children with ASD who also had gastrointestinal problems or had previously had a developmental regression were more likely to use a gluten free diet. This study demonstrates that gluten free diets are commonly used among children with ASD. More research is needed on the effectiveness of a gluten free diet in managing both gastrointestinal and behavioral symptoms related to ASD.

Associations between Parental Broader Autism Phenotype and Child Autism Spectrum Disorder Phenotype in the Study to Explore Early Development.

Rubenstein E, Wiggins LD, Schieve LA, Bradley C, DiGuiseppi C, Moody E, Pandey J, Pretzel RE, Howard AG, Olshan AF, Pence BW, Daniels J.

Autism, 2018

This study assessed how the variation in developmental features among children with ASD was related to their parents' own autism-related traits. The presence of autism traits in family members of children with ASD is commonly referred to as the "broader autism phenotype" or BAP. The study findings show that if one or both parents have traits consistent with BAP, the child's ASD is more likely to fall within a certain clinical presentation than if neither parent has traits consistent with BAP. This clinical presentation in the child is characterized by average nonverbal abilities, mild language and motor delays, and increased frequency of other co-occurring developmental difficulties such as anxiety, depression, aggression, and attention difficulties. The findings reported in this study could help better our understanding of the genetics of ASD.

Studies that Used SEED Data to Evaluate Clinical and Laboratory Methods

In addition to research on ASD risk factors and on the developmental characteristics and health outcomes of children with ASD or other developmental disabilities, the wealth of data collected in SEED has allowed researchers to address critical gaps in our understanding of the performance of various ASD screening and assessment tools and to contribute to the development of genetic laboratory tests.

Influence of Family Demographic Factors on Social Communication Questionnaire Scores.

Rosenberg SA, Moody EJ, Lee LC, DiGuiseppi C, Windham GC, Wiggins LD, Schieve LA, Ledbetter CM, Levy SE, Blaskey L, Young L, Bernal P, Rosenberg CR, Fallin MD.

Autism Research, 2018

This study assessed how the responses to a standardized questionnaire to screen for autism symptoms varied by family demographic characteristics. The study findings indicate that test performance was different in families with an indication of low versus higher socioeconomic status. These findings are important for both researchers and clinicians using autism screening questionnaires; they should be mindful that these tools might perform differently in various sociodemographic groups of children and their parents.

Screening for Autism with the SRS and SCQ: Variations across Demographic, Developmental and Behavioral Factors in Preschool Children.

Moody EJ, Reyes N, Ledbetter C, Wiggins L, DiGuiseppi C, Alexander A, Jackson S, Lee LC, Levy SE, Rosenberg SA.

Journal of Autism and Developmental Disorders, 2017

This study assessed and compared the performance of two standardized questionnaires to screen for autism symptoms. The accuracy of each questionnaire varied depending on the child's level of developmental functioning and family sociodemographic traits. For example, the instruments were less accurate when children had high levels of challenging behaviors or lower levels of developmental functioning. Test performance also varied in families with indication of lower versus higher socioeconomic status. These findings are important for both researchers and clinicians using autism screening questionnaires; they should be mindful that these tools perform differently in various sociodemographic groups of children and their parents.

The Broader Autism Phenotype in Mothers is Associated with Increased Discordance Between Maternal-Reported and Clinician-Observed Instruments that Measure Child Autism Spectrum Disorder.

Rubenstein E, Edmondson Pretzel R, Windham GC, Schieve LA, Wiggins LD, DiGuiseppi C, Olshan AF, Howard AG, Pence BW, Young L, Daniels J.

Journal of Autism and Developmental Disorders, 2017

This study assessed whether parents who have autism traits reported their children's potential autism symptoms in a similar way as parents without an indication of autism traits. The findings indicate that parents with autism traits report more autism traits in their children compared to parents without autism traits, but parent reports do not always match clinician assessments based on observed behaviors in the child. It is possible that parents with some autism traits are more adept at identifying subtle characteristics of autism in their child. Another possible explanation for the study findings is that questions on various child behaviors could be interpreted differently by parents with and without autism traits. Further study is needed. The findings reported in this study could help better our understanding of developmental assessment results in young children.

"Gap Hunting" to Characterize Clustered Probe Signals in Illumina Methylation Array Data.

Andrews SV, Ladd-Acosta C, Feinberg AP, Hansen KD, Fallin MD.

Epigenetics & Chromatin, 2016

This study assessed new laboratory approaches to analyzing information on genetics collected through SEED. The findings contribute to the growing literature on how genes and environmental factors might interact in a way that increases the risk for ASD. While this study does not directly study these interactions, researchers describe and demonstrate how new laboratory approaches could help identify genetic associations.

Studies that Used SEED Data in Combination with Data from Other Studies to Better Understand ASD Risk Factors

Cross-tissue Integration of Genetic and Epigenetic Data Offers Insight into Autism Spectrum Disorder.

Andrews SV, Ellis SE, Bakulski KM, Sheppard B, Croen LA, Hertz-Picciotto I, Newschaffer CJ, Feinberg AP, Arking DE, Ladd-Acosta C, Fallin MD.

Nature Communications, 2017

In this study, researchers used SEED data and data from other studies to learn more about genetics and genetic regulation in children with ASD. While it is well-understood that genetics are related to ASD, many unanswered questions remain, such as how certain genes are turned on or off. The information from this study provides insights about how certain genes might be related to ASD.

Pleiotropic Mechanisms Indicated for Sex Differences in Autism.

Mitra I, Tsang K, Ladd-Acosta C, Croen LA, Aldinger KA, Hendren RL, Traglia M, Lavillaureix A, Zaitlen N, Oldham MC, Levitt P, Nelson S, Amaral DG, Hertz-Picciotto I, Fallin MD, Weiss LA.

PLOS Genetics, 2016

In this study, researchers used SEED data and data from other studies to investigate sex-specific genetic effects for ASD. The findings indicate involvement of genes on the X chromosome. These findings help us better understand how ASD might differ in girls and boys.