



Published in final edited form as:

Res Dev Disabil. 2021 May ; 112: 103897. doi:10.1016/j.ridd.2021.103897.

Evaluation of sex differences in preschool children with and without autism spectrum disorder enrolled in the study to explore early development

Lisa D. Wiggins^{a,*}, Eric Rubenstein^b, Gayle Windham^c, Brian Barger^d, Lisa Croen^e, Nicole Dowling^a, Ellen Giarelli^f, Susan Levy^g, Eric Moody^h, Gnakub Soke^a, Victoria Fields^a, Laura Schieve^a

^aNational Center on Birth Defects and Developmental Disabilities, Centers for Disease Control and Prevention, Atlanta, GA, United States

^bBoston University, Department of Epidemiology, Boston, MA, United States

^cCalifornia Department of Public Health, Environmental Health Investigations Branch, Richmond, CA, United States

^dGeorgia State University, School of Public Health, Atlanta, GA, United States

^eKaiser Permanente Northern California, Division of Research, Autism Research Program, Oakland, CA, United States

^fCollege of Nursing and Health Professionals, Drexel University, Philadelphia, PA, United States

^gCenter for Autism Research, Children's Hospital of Philadelphia, Philadelphia, PA, United States

^hUniversity of Wyoming, Wyoming Institute for Disabilities College of Health Sciences, Laramie, WY, United States

Abstract

Background and aims: Research in school-aged children, adolescents, and adults with autism spectrum disorder (ASD) has found sex-based differences in behavioral, developmental, and diagnostic outcomes. These findings have not been consistently replicated in preschool-aged children. We examined sex-based differences in a large sample of 2–5-year-old children with ASD symptoms in a multi-site community-based study.

Methods and procedures: Based on a comprehensive evaluation, children were classified as having ASD (n = 1480, 81.55 % male) or subthreshold ASD characteristics (n = 593, 70.15 %

*Corresponding author at: National Center on Birth Defects and Developmental Disabilities, Centers for Disease Control and Prevention, 4770 Buford Highway NE S106-4, Atlanta, GA, 30341, United States. lwiggins@cdc.gov (L.D. Wiggins).
CRediT authorship contribution statement

Lisa D. Wiggins: Conceptualization, Writing -original draft, Methodology, Writing -review & editing. **Eric Rubenstein:** Formal analysis, Methodology, Writing -review & editing. **Gayle Windham:** Methodology, Writing -review & editing. **Brian Barger:** Methodology, Writing -review & editing. **Lisa Croen:** Methodology, Writing -review & editing. **Nicole Dowling:** Methodology, Writing -review & editing. **Ellen Giarelli:** Methodology, Writing -review & editing. **Susan Levy:** Methodology, Writing -review & editing. **Eric Moody:** Methodology, Writing -review & editing. **Gnakub Soke:** Methodology, Writing -review & editing. **Victoria Fields:** Validation, Methodology, Writing -review & editing. **Laura Schieve:** Methodology, Writing -review & editing.

Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:<https://doi.org/10.1016/j.ridd.2021.103897>.

male). Outcomes were behavior problems, developmental abilities, performance on ASD screening and diagnostic tests, and parent-reported developmental conditions diagnosed before study enrollment.

Outcomes and results: We found no statistically significant sex differences in behavioral functioning, developmental functioning, performance on an ASD screening test, and developmental conditions diagnosed before study enrollment among children with ASD or subthreshold ASD characteristics. Males in both study groups had more parent reported restricted interests and repetitive behaviors than females, but these differences were small in magnitude and not clinically meaningful.

Conclusions and implications: Preschool males and females who showed risk for ASD were more similar than different in the outcomes assessed in our study. Future research could examine sex-based differences in ASD phenotypes as children age.

Keywords

Autism; Children; Female; Male; Gender; Sex

1. Introduction

Autism spectrum disorder (ASD) is a developmental disability characterized by deficits in social-communication and the presence of restricted interests and repetitive behaviors (RRB) that emerge in early childhood (American Psychiatric Association, 2013). The estimated prevalence of ASD in U.S. school children aged 8 years in 2016 was 29.7 per 1000 males and 6.9 per 1000 females, resulting in a male-to-female prevalence ratio of 4.3 (Maenner et al., 2020). The preponderance of males versus females with recognized ASD has led some to question whether there are ascertainment and diagnostic biases that may partially account for the skewed male-to-female prevalence ratio (Halladay et al., 2015). Specifically, females with ASD may have a different behavioral, developmental, and diagnostic profiles than males with ASD that delay the identification of ASD symptoms (Lai, Lombardo, Auyeung, Chakrabarti, & Baron-Cohen, 2015). Questions regarding sex-specific biases have led to a call for research that addresses differences in biological, behavioral, and diagnostic phenotypes of males and females with ASD (Interagency Autism Coordinating Committee (IACC), 2017).

Existing research on sex-based diagnostic bias in ASD has explored reasons why males and females may come to the attention of healthcare providers, have differential performance on screening and diagnostic tests, and display variations in ASD phenotypes. Some studies found that more females than males with ASD have co-occurring intellectual disability (ID; Baio et al., 2018; Frazier, Georgiades, Bishop, & Hardan, 2015; Hiller, Young, & Weber, 2014; Rivet & Matson, 2011), which could suggest that many females without ID remain unidentified. One study found that parent-reported concerns with emotional and behavioral problems were more predictive of an ASD diagnosis in females whereas parent-reported RRB was more predictive of an ASD diagnosis in males (Duvekot et al., 2017). These findings coincide with other studies that found RRB are more often observed and reported in males than females on diagnostic instruments (Mandy et al., 2012; Van Wijngaarden-

Cremers et al., 2014). Sex-specific characteristics may therefore result in an overrepresentation of females with ASD and co-occurring ID, behavioral problems, or emotional problems in clinical and research practice. Sex-specific characteristics may also result in an under-representation of females with RRB that are not typically ascertained during diagnostic evaluation.

Many previous studies that report sex-based differences in ASD phenotypes have focused on school-aged children, adolescents, and adults with ASD. Findings from these studies have raised concerns that sex-based differences in early childhood could impede early identification and treatment of young females with ASD. The Autism Diagnostic Observation Schedule (ADOS) and Autism Diagnostic Interview–Revised (ADI-R) are considered gold-standard diagnostic instruments, but both have disproportionately more males than females in validation studies when compared to the general population. Consequently, the ADOS and ADI-R may have a bias toward male social and behavioral development and lack sensitivity in detecting characteristics of ASD in females (Adamou, Johnson, & Alty, 2018; Duvekot et al., 2017). Females not recognized with ASD early on may then miss opportunities for interventions that capitalize on neuroplasticity to improve developmental outcomes (Dawson, 2008; Giarelli et al., 2010; Shattuck et al., 2009).

However, several studies of preschool-aged children have found no significant differences in developmental functioning among males and females with ASD (Andersson, Gillberg, & Miniscalco, 2013; Lawson, Joshi, Barbaro, & Dissanayake, 2018; Postorino et al., 2015; Reinhardt, Wetherby, Schatschneider, & Lord, 2015). Andersson et al. (2013) evaluated children at 23–33 months of age and then again at 36–59 months of age, with an average time between assessments of 24 months. There were no significant differences between males and females with ASD in overall cognitive abilities, verbal abilities, or non-verbal abilities. Other studies have found no sex differences in behavioral functioning in preschool-aged children with ASD (Hartley & Sikora, 2009; Lawson et al., 2018; Postorino et al., 2015). Research on sex-based differences in ASD symptom presentation in young children is more varied, although most studies report no differences in social communication (Andersson et al., 2013; Reinhardt et al., 2015), RRB (Andersson et al., 2013; Lawson et al., 2018; Reinhardt et al., 2015), or overall ASD symptom severity (Andersson et al., 2013; Postorino et al., 2015; Reinhardt et al., 2015) based on child sex.

ASD symptoms exist on a continuum within the general population and those at one extreme qualify for an ASD diagnosis. Since many children with ASD are not diagnosed until they enter school, and females may experience delayed ASD diagnosis, there is a need to include preschool-aged children with diverse ASD symptoms in research samples. The Study to Explore Early Development (SEED) provides such a sample. SEED is an ongoing multi-site, community-based study that was designed to identify the development and risk factors of ASD in 2–5-year-old children (Schendel et al., 2012). Children were screened and evaluated for ASD and some met stringent study criteria for ASD while others were classified as having subthreshold ASD characteristics. The SEED sample thus offers a unique opportunity to evaluate behavioral, developmental, and diagnostic differences among males and females with a range of ASD symptoms in early development.

1.1 Study objectives and hypotheses

The objectives of this study were threefold: (1) evaluate sex-based differences in behavior problems and developmental abilities among children who were evaluated for ASD in SEED and ultimately classified as ASD or subthreshold ASD characteristics (2) explore sex-based differences among these children in terms of performance on an ASD screening test and two diagnostic tests, and (3) explore sex-based differences among these children in parent-reported developmental diagnoses given before study enrollment. Based on previous research in young samples of children, we did not expect to find sex-based differences in behavioral or developmental functioning, social deficits or RRB, or parent-reported diagnoses given before study enrollment.

2. Methods

Participants were children and their families enrolled in SEED. Children were born between September 1, 2003 and August 31, 2006 (Phase 1) and January 1, 2008–December 31, 2011 (Phase 2) and met initial screening criteria for ASD risk. SEED was funded by the Centers for Disease Control and Prevention (CDC) and was conducted in six study sites across the U.S., located in communities in California, Colorado, Georgia, North Carolina, Maryland, and Pennsylvania. The SEED protocols were approved by Institutional Review Boards at each site and CDC.

2.1. Procedures

SEED enrollment focused on three groups of children: (1) those with an existing ASD diagnosis identified from multiple educational and health providers or family or physician referral, (2) those with an existing non-ASD developmental delay or disorder identified from multiple educational and health providers or family or physician referral, and (3) those randomly sampled from the general population and identified from state birth records. Children eligible for SEED were enrolled between 2–5 years of age, were born and resided in one of the six study areas, and lived with a caregiver who was competent to communicate in English (or in California and Colorado, in English or Spanish). Children were excluded from the study if their caregiver noted they had a vision, hearing, or movement impairment that would prevent their participation in a developmental evaluation. Caregivers of enrolled children gave written consent to participate in the study. Schendel et al. (2012) provides a detailed description of eligibility criteria, ascertainment methods, enrollment methods, and data collection procedures in SEED.

All children were screened for ASD with the Social Communication Questionnaire (SCQ) via telephone interview upon study enrollment. Mothers completed a separate telephone interview about their pregnancy history and their child's existing diagnoses. Mothers also completed questionnaires about the health and functioning of their child. Children completed an in-person clinic visit comprised of an early learning test. Children in this sample also met one of three criteria: (1) screened positive for ASD risk using a SCQ cut-off score of 11 points, (2) had an existing ASD diagnosis reported during a caregiver interview, or (3) had ASD-specific behaviors noted during the early learning test. These children were administered the ADOS and a caregiver was administered the ADI-R for further evaluation.

The sample of children in these analyses thus were a subset of SEED participants who demonstrated ASD risk and were evaluated for ASD regardless of previous ASD diagnosis.

SEED ASD case status was based on the results of the ADI-R and ADOS instead of clinical judgment to offer a consistent, uniform case definition across study sites. Children classified as ASD were those who met ASD criteria on both the ADOS and ADI-R, or who met ASD criteria on the ADOS and one of three alternate criteria on the ADI-R. The alternate ADI-R criteria were (1) met criteria on the social domain (10 points) and was within two points of meeting criteria on the communication domain (eight points for verbal children and seven points for nonverbal children), (2) met criteria on the communication domain and was within two points on the social domain, or (3) met criteria on the social domain and was within one point of meeting criteria on the behavioral domain (three points). Children classified as subthreshold characteristics had an SCQ score of ≥ 11 points or existing ASD diagnosis but did not meet the stringent study criteria for ASD. The SEED classification criteria had a satisfactory balance of sensitivity (0.86) and specificity (0.74) when compared to clinical judgment of whether the child had ASD or another DD (Wiggins et al., 2015). Kappa agreement between SEED classification criteria and clinical judgment was 0.71, reflecting substantial agreement (Wiggins et al., 2015).

2.2. Measures

2.2.1 Behavioral and developmental functioning

Child Behavior Checklist/1½–5 Years (CBCL).: The CBCL (Achenbach, 1992) is a standardized checklist that contains 99 behaviors rated by the caregiver as “never true”, “sometimes true”, or “often true.” Internalizing behavior problems are defined by items assessing emotional reactivity, anxiety/depression, somatic complaints, and withdrawn behaviors. Externalizing behavior problems are defined by items assessing attention problems and aggressive behavior. CBCL externalizing and internalizing *t*-scores of 60 or higher indicate borderline to clinically significant problems in the child.

Mullen Scales of Early Learning (MSEL).: The MSEL (Mullen, 1995) is a standardized in-person evaluation of the early learning abilities of young children. The MSEL early learning composite is a standard score based on performance in four domains: visual reception, fine motor, expressive language, and receptive language. MSEL domain *t*-scores have a mean of 50 and standard deviation of 10; *t*-scores less than 40 points indicate below average functioning in the child compared to other children the same age. Early learning composite standard scores have a mean of 100 and standard deviation of 15; children with standard scores less than 70 points on the MSEL were defined as having ID.

2.2.2. Autism screening and diagnostic tests

Social Communication Questionnaire (SCQ).: The SCQ (Rutter, Bailey, & Lord, 2003) is a standardized parent checklist that has 40 items rated as “true” or “not true.” Total scores range from 0 to 39 with higher scores representing more social communication impairment. The SCQ performs adequately in both males and females (Evans, Boan, Bradley, & Carpenter, 2019; Moody et al., 2018). The SCQ recommends that scores of 15 or higher are indicative of ASD risk. However, sensitivity and specificity of the SCQ is maximized at a

cutoff of 11 points when used with younger children (Wiggins, Bakeman, Adamson, & Robins, 2007).

Autism Diagnostic Interview Revised (ADI-R): The ADI-R (Lord, Rutter, & Le Couteur, 1994) is a semi-structured diagnostic interview used to classify children as ASD or non-ASD. The ADI-R allows clinicians to gather comprehensive information about the child from a caregiver in three domains of development: social, communication, and restricted and repetitive behaviors (RRB). The range of scores possible are 0–30 for the social domain (with a diagnostic cutoff of 10 points), 0–26 for the communication domain (with a diagnostic cutoff of eight for verbal children and seven for nonverbal children), and 12 for the RRB domain (with a diagnostic cutoff of three points).

Autism Diagnostic Observation Schedule (ADOS): The ADOS (Gotham, Pickles, & Lord, 2009; Lord, Rutter, DiLavore, & Risi, 1999) is a standardized diagnostic observation used to classify children as ASD or non-ASD. During an ADOS administration, the clinician tries to elicit communication and social interaction using structured play activities. Behaviors observed during the ADOS are coded in two domains: social affect and RRB. The range of scores possible are 0–20 points for the social domain and 0–8 points for the RRB domain (the diagnostic cutoff scores range from 7 to 11 and are dependent on age and language abilities of the child). ADOS classification (i.e., ASD or non-ASD) is determined by the total score, which is converted into a calibrated severity score that ranges from 1 (minimal ASD symptoms) to 10 (severe ASD symptoms).

2.2.3. Existing child diagnoses

Caregiver interview (CGI): The CGI was developed by SEED study staff to ascertain the health of the index child's mother before, during, and shortly after her pregnancy and the developmental history of the child. Data relevant to this analysis include questions on existing child developmental diagnoses given before study enrollment. Interviewers asked mothers (or other caregiver if the mother was not available [~2%]) "Has a doctor or healthcare provider ever told you that your child had one of the following conditions?" The condition list was comprised of attention deficit hyperactivity disorder (ADHD), ASD, cerebral palsy, developmental delay, Down Syndrome, hearing impairment, language delay, motor delay, and vision problems. A child was considered to have an existing ASD diagnosis if a caregiver indicated the child had been diagnosed with ASD on the enrollment call, reported ASD in the CGI, or if the child had a health billing code of 299.X (ascertained in California and Georgia from healthcare providers before study enrollment).

2.3. Statistical analyses

Sex differences in CBCL, MSEL, SCQ, ADI-R, and ADOS scores were evaluated using ANOVA analyses. ANOVA analyses were used instead of t-tests to yield eta squared (η^2) effect sizes for ease of interpretation. Eta squared is a measure of the strength of an association between variables. In this study, eta squared can be described as the proportion of the total variance in a dependent variable (e.g., developmental abilities) that is associated with child sex. There is no agreed upon standard of what magnitude of effect is clinically or practically meaningful. Most researchers use the most liberal recommendations offered by

Cohen (1988): an eta squared of at least 0.01 is needed to assume a small effect and an eta squared of at least 0.06 is needed to assume a moderate effect of the independent variable. Eta squared effect sizes were used to interpret clinical versus statistical significance.

Sex differences in the presence of an existing diagnosis of ADHD, ASD, cerebral palsy, developmental delay, Down Syndrome, hearing impairment, language delay, motor delay, and vision problems were evaluated with chi square tests. Cramer's V statistic was reported as a measure of magnitude of association and used to interpret clinical versus statistical significance. Like eta squared, Cramer's V is described as the proportion of the total variance in a dependent variable (e.g., diagnosis of ASD before study enrollment) that is associated with child sex. A Cramer's V estimate of at least 0.20 is needed to assume a small effect and a Cramer's V of at least 0.30 is needed to assume a moderate effect of the independent variable (Cohen, 1988).

To account for false discovery in chi square tests, we used the Benjamini Hochberg procedure with $\alpha = 0.05$ (Benjamini & Hochberg, 1995). This procedure helps to avoid Type 1 errors by correcting for false discovery while maintaining adequate power. First, p values were ranked from lowest to highest within each study group. Second, critical values were calculated by dividing the rank of an individual p value by number of hypotheses tested, then multiplied by the false discovery rate. We did this correction for developmental conditions, ranking and comparing nine p values in each group (for example, significance threshold for lowest p value = $0.05 * 1/9 = 0.006$).

All analyses were then stratified by whether the child had an existing ASD diagnosis and whether the child had ID, as defined by the MSEL. Stratified analyses were secondary in nature and were conducted to assess whether an existing child ASD diagnosis or ID confounded results. They are therefore discussed briefly in text and presented as a data supplement.

3. Results

3.1. Sample characteristics

There were 2073 children who were evaluated for ASD in SEED. After the in-person evaluation, 1480 (81.55 % male) met SEED criteria for ASD and 593 (70.15 % male) were classified as having subthreshold ASD characteristics. Median age at child evaluation was 56 months and did not differ by sex in either study group. Most mothers were ≥ 35 years old at study enrollment, white non-Hispanic, and had a college degree or higher. There were no statistically significant sex differences among children with ASD or subthreshold ASD characteristics in maternal age, maternal education, maternal race/ethnicity, or study site (Table 1).

3.2. Behavioral and developmental functioning

In the ASD group, there were no statistically differences between male and female children in CBCL internalizing behavior t -scores, CBCL externalizing behavior t -scores, MSEL early learning composite standard scores, MSEL expressive language t -scores, MSEL fine motor t -scores, MSEL receptive language t -scores, or MSEL visual reception t -scores (Table 2).

Similarly, there were no statistically significant differences between male and female children with subthreshold ASD characteristics on CBCL or MSEL scores (Table 2).

3.3. Autism screening and diagnostic tests

There were no statistically significant differences between male and female children in either study group based on SCQ total scores (Table 3). Males in the ASD group had more RRB than females reported on the ADI-R and observed on the ADOS (Table 3). Males with subthreshold ASD characteristics had more RRB reported on the ADI-R but not observed on the ADOS, more social deficits observed on the ADOS but not reported on the ADI-R, and more total ASD severity observed on the ADOS than females (Table 3). The measures of association related to these differences were small in magnitude (e.g., the largest eta squared value was the minimum suggested by Cohen (1988) to assume a small effect of the independent variable [0.01]).

3.4. Parent-reported developmental diagnoses before study enrollment

In the ASD group, there were no statistically significant sex-based differences in parent report of existing child diagnoses after correction for false discovery (Table 4). There were also no sex-based differences in parent report of any developmental diagnosis given before study enrollment among children with subthreshold ASD characteristics after the correction for false discovery (Table 5).

3.5. Analyses by presence of a previous ASD diagnosis and intellectual disorder

Analyses stratified by the presence of a previous ASD diagnosis or ID supported our main findings in that there were very few sex differences and those that were statistically significant had small measures of association (Supplemental Tables 1–6). Stratified analyses most consistent with unstratified analyses were that males with a previous ASD diagnosis in both study groups had more RRB reported on the ADI-R than males without a previous ASD diagnosis. Males with ID in both study groups had more RRB reported on the ADI-R than males without ID. The measures of association related to these differences were small.

4. Discussion

Our study explored sex-based differences between preschool-aged males and females evaluated for ASD in SEED. We found no statistically significant sex differences in sample characteristics, behavioral functioning, developmental functioning, or total score on an ASD screening test in either those with ASD or subthreshold ASD characteristics. The few sex differences found in ADOS and ADI-R domain scores were of small magnitude and were not clinically meaningful. There were no statistically significant sex differences in any developmental condition diagnosed before study enrollment after correction for false discovery. We therefore conclude that males and females with ASD symptoms were more similar than different in our study.

Children with ASD who are evaluated and diagnosed in the preschool years are more likely to have co-occurring conditions such as ID and language delay than those diagnosed later in life (Shattuck et al., 2009). Most children with ASD in our sample had co-occurring ID (63.7

%; Supplemental Table 1) and parent-reported language delays (66.7 % for males and 63.8 % for females; Table 4). Most children with subthreshold characteristics *did not have* co-occurring ID (66.8 %; Supplemental Table 2) but did have parent-reported language delays (64.9 % for males and 67.8 % for females; Table 5). It is possible that sex-differences are negligible in young children with ASD symptoms and language delays – despite overall cognitive functioning – who come to the attention of healthcare providers early in life. Sex-based differences may then emerge or become more apparent as children age.

It is important to recognize and treat both males and females with diverse ASD phenotypes as early as possible. Early intervention services can improve adaptive and overall cognitive functioning and reduce challenging behaviors such as aggression (Estes et al., 2015; Kasari, Gulsrud, Wong, Kwon, & Locke, 2010; Noyes-Grosser et al., 2018; Rotholz, Kinsman, Lacy, & Charles, 2017). An ASD diagnosis can empower families to advocate for services for their child (Kasari et al., 2010; Noyes-Grosser et al., 2018). An ASD diagnosis can also provide parents with important information about child behavior and development and a reason for the challenges they may have faced with parenting (Autism Speaks, 2020). Enhanced developmental surveillance and screening of early social behaviors in addition to language behaviors may help detect more children with ASD in early development. CDC’s “Learn the Signs. Act Early” surveillance checklists include separate sections for social milestones; screening instruments such as the Ages and Stages Questionnaire: Social Emotional, 2nd edition focus specifically on social development (Squires, Bricker, & Twombly, 2015).

Correcting for false discovery and reporting the magnitude of associations enhanced the interpretation of our findings. Alone, p values are influenced by sample size and do not communicate the magnitude of an association or imply clinical importance (Dahiru, 2008; Sullivan & Feinn, 2012). The sex differences deemed statistically significant by p values in these analyses had small magnitudes of association and were therefore not robust or clinically meaningful. For instance, males with ASD had a significantly higher ADI-R RRB scores than females with ASD ($p < .01$). However, the largest effect size was the minimum suggested by Cohen (1988) to assume a small effect of child sex (.01).

It has been reported that sex differences in the presence of RRB become more clinically meaningful after six years of age (Van Wijngaarden-Cremers et al., 2014). The nature of RRB in individuals with ASD who are school-aged and older may also differ based on sex. Hiller, Young, and Weber (2014) found that males with ASD were more likely to be overly interested in wheeled toys and females with ASD were more likely to be overly interested in stickers and pens. Sutherland, Hodge, Bruck, Costly, and Klieve (2017) found that males with ASD showed more restricted interests in transportation, technology, and dinosaurs than females with ASD. Females with ASD showed more restricted interests in music, art, and books than males with ASD. These findings suggest that specialized interests may coincide with traditional gender lines once a child with ASD enters school. ASD screening and diagnostic instruments may therefore need to consider a broader range of restricted interests in school-aged children.

Sex differences in certain social deficits may also be more relevant to school-aged children with ASD than preschool-aged children with ASD. One example is social “camouflaging.” Some studies have found that school-aged females with ASD have more desire for social interaction and more “camouflaging” or masking of their ASD symptoms than males, even though social deficits are similar between sexes (Dean, Harwood, & Kasari, 2017; Schuck, Flores, & Fung, 2019). Compensatory behaviors used by females with ASD to mask their social challenges are staying in close proximity to peers and moving from one social activity to another (Dean et al., 2017). Females with ASD might learn these strategies because they are socialized to be more outgoing than males (Schuck et al., 2019). Another possible explanation for social camouflaging is that females with ASD and outward social deficits may face more stigma than males, and thus compensate to reduce that stigma. Probing for social deficits despite the desire for social interaction and evaluating active or passive camouflaging of ASD behaviors may help identify more school-aged females with ASD characteristics.

4.1. Study limitations

There are two main limitations associated with these analyses. First, only children who showed ASD risk on a screening test, had a known previous ASD diagnosis, or had ASD-specific behaviors noted during a cognitive test were evaluated for ASD in SEED. Some children without ASD risk may have been classified as ASD or subthreshold ASD characteristics if they had been evaluated. Second, both children with ASD and children with subthreshold ASD characteristics had below average MSEL language skills and most had a parent-reported diagnosis of language delay. Different results may be obtained in samples of preschool-aged children with more advanced language skills.

4.2. Study conclusion

Our findings support previous research that found negligible sex differences in behavioral, developmental, and diagnostic outcomes in preschool-aged children with ASD and those with subthreshold ASD characteristics. We conclude that males and females with ASD symptoms were more similar than different in our study. Future research could explore sex-based similarities and differences in children with ASD symptoms as they age.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgements and funding source

We would like to thank SEED study staff and the children and families who participated in the study. We would also like to thank the SEED Data Coordinating Center team at the Clinical and Translational Sciences Institute of Michigan State University for their support throughout this study. This publication was supported by six cooperative agreements from the Centers for Disease Control and Prevention (CDC): Cooperative Agreement Number U10DD000180, Colorado Department of Public Health; Cooperative Agreement Number U10DD000181, Kaiser Foundation Research Institute (CA); Cooperative Agreement Number U10DD000182, University of Pennsylvania; Cooperative Agreement Number U10DD000183, Johns Hopkins University; Cooperative Agreement Number U10DD000184, University of North Carolina at Chapel Hill; and Cooperative Agreement Number U10DD000498, Michigan State University. The findings and conclusions in this report are those of the authors and do not necessarily represent the official position of the Centers for Disease Control and Prevention.

References

- Achenbach T. (1992). Child behavior checklist. Burlington, VT: Achenbach System of Empirically Based Assessment.
- Adamou M, Johnson M, & Alty B. (2018). Autism Diagnostic Observation schedule (ADOS) scores in males and females diagnosed with autism: A naturalistic study. *Advances in Autism*, 4(2), 49–55.
- American Psychiatric Association. (2013). Diagnostic and statistical manual of mental disorders (5th ed.). Arlington, VA: American Psychiatric Publishing.
- Andersson GW, Gillberg C, & Miniscalco C. (2013). Preschool children with suspected autism spectrum disorders: Do girls and boys have the same profiles? *Research in Developmental Disabilities*, 34(1), 413–422. [PubMed: 23023300]
- Autism Speaks. (2020). 100-day kit for families of young children recently diagnosed with autism. Retrieved from: <https://www.autismspeaks.org/tool-kit/100-day-kit-young-children>.
- Baio J, Wiggins LD, Christensen DL, Daniels J, Warren Z, Kurzius-Spencer M, ... Dowling NF (2018). Prevalence of autism spectrum disorder among children aged 8 years – Autism and Developmental Disabilities Monitoring Network, 11 sites, United States, 2014. *Morbidity and Mortality Weekly Report*, 67(6), 1–23. [PubMed: 29324727]
- Benjamini Y, & Hochberg Y. (1995). Controlling the false discovery rate: A practical and powerful approach to multiple testing. *Journal of the Royal Statistical Society Series B*, 57(1), 289–300.
- Cohen J. (1988). *Statistical power analysis for the behavioral sciences* (2nd edition). Routledge.
- Dahiru T. (2008). P-value, a true test of statistical significance? A cautionary note. *Annals of Ibadan Postgraduate Medicine*, 6(1), 21–26.
- Dawson G. (2008). Early behavioral intervention, brain plasticity, and the prevention of autism spectrum disorder. *Developmental Psychopathology*, 20(3), 775–803.
- Dean M, Harwood R, & Kasari C. (2017). The art of camouflage: Gender differences in the social behaviors of girls and boys with autism spectrum disorder. *Autism*, 21, 678–689. [PubMed: 27899709]
- Duvekot J, van der Ende J, Verhulst FC, Slappendel G, van Daalen E, Maras A, ... Greaves-Lord K. (2017). Factors influencing the probability of a diagnosis of autism spectrum disorder in girls versus boys. *Autism*, 21(6), 646–658. [PubMed: 27940569]
- Estes AE, Munson J, Rogers SJ, Greenson J, Winter J, & Dawson G. (2015). Long-term outcomes of early intervention in 6-year-old children with autism spectrum disorder. *Journal of the American Academy of Child and Adolescent Psychiatry*, 54(7), 580–587. [PubMed: 26088663]
- Evans SC, Boan AD, Bradley C, & Carpenter LA (2019). Sex/gender differences in screening for autism spectrum disorder: Implications for evidence-based assessment. *Journal of Clinical Child and Adolescent Psychiatry*, 48(6), 840–854.
- Frazier TW, Georgiades S, Bishop SL, & Hardan AY (2015). Behavioral and cognitive characteristics of females and males with autism in the Simons Simplex Collection. *Journal of the American Academy of Child and Adolescent Psychiatry*, 53(3), 329–340.
- Giarelli E, Wiggins LD, Rice E, Levy S, Kirby R, Pinto-Martin J, ... Mandell D. (2010). Sex differences in the evaluation and diagnosis of autism spectrum disorders among children. *Disability and Health Journal*, 3(2), 107–116. [PubMed: 21122776]
- Gotham K, Pickles A, & Lord C. (2009). Standardizing ADOS scores for a measure of severity in autism spectrum disorders. *Journal of Autism and Developmental Disorders*, 39(5), 693–705. [PubMed: 19082876]
- Halladay AK, Bishop S, Constantino JN, Daniels AM, Koenig K, Palmer K, Messinger D, ... Szatmari P. (2015). Sex and gender differences in autism spectrum disorder: Summarizing evidence gaps and identifying emerging areas of priority. *Molecular Autism*, 6(36), 1–5. [PubMed: 25705365]
- Hartley S, & Sikora D. (2009). Sex differences in autism spectrum disorder: an examination of developmental functioning, autistic symptoms, and coexisting behavior problems in toddlers. *Journal of Autism and Developmental Disorders*, 39, 1715–1722. [PubMed: 19582563]
- Hiller RM, Young RL, & Weber N. (2014). Sex differences in autism spectrum disorder based on DSM-5 criteria: Evidence from clinical and teacher reporting. *Journal of Abnormal Child Psychology*, 42(8), 1381–1393. [PubMed: 24882502]

- Interagency Autism Coordinating Committee (IACC). (2017). 2016–2017 interagency autism coordinating committee strategic plan for autism Spectrum disorder. 10. Retrieved from website: the U.S. Department of Health and Human Services Interagency Autism Coordinating Committee <https://iacc.hhs.gov/publications/strategic-plan/2017>.
- Kasari C, Gulsrud AC, Wong C, Kwon S, & Locke J. (2010). Randomized controlled caregiver mediation joint engagement intervention for toddlers with autism. *Journal of Autism and Developmental Disorders*, 40(9), 1045–1056. [PubMed: 20145986]
- Lai MC, Lombardo MV, Auyeung B, Chakrabarti B, & Baron-Cohen S. (2015). Sex/Gender differences and autism: Setting the scene for future research. *Journal of the American Academy of Child and Adolescent Psychiatry*, 54, 11–24. [PubMed: 25524786]
- Lawson LP, Joshi R, Barbaro J, & Dissanayake C. (2018). Gender differences during toddlerhood in autism spectrum disorder: A prospective community-based longitudinal follow-up study. *Journal of Autism and Developmental Disorders*, 48(8), 2619–2628. [PubMed: 29497988]
- Lord C, Rutter M, DiLavore PC, & Risi S. (1999). *Autism diagnostic observation schedule*. Los Angeles, CA: Western Psychological Services.
- Lord C, Rutter M, & Le Couteur AL (1994). Autism diagnostic interview-revised: A revised version of a diagnostic interview for caregivers of individuals with possible pervasive developmental disorders. *Journal of Autism and Developmental Disorders*, 24(5), 659–685. [PubMed: 7814313]
- Maenner M, Shaw K, Baio J, Washington A, Patrick M, DiRienzo M, et al. (2020). Prevalence of autism spectrum disorder among children aged 8 years — autism and developmental disabilities monitoring network, 11 sites, United States, 2016. *MMWR Surveillance Summaries*, 69, 1–12.
- Mandy W, Chilvers R, Chowdhury U, Salter G, Seigal A, & Skuse D. (2012). Sex differences in autism spectrum disorder: Evidence from a large sample of children and adolescents. *Journal of Autism and Developmental Disorders*, 42(7), 1304–1313. [PubMed: 21947663]
- Moody EJ, Reyes N, Ledbetter C, Wiggins LD, DiGuseppi C, Alexander A, ... Rosenberg S. (2018). Screening for autism with the SRS and SCQ: Variations scores demographic, developmental, and behavioral factors in preschool children. *Journal of Autism and Developmental Disorders*, 47(11), 3550–3561.
- Mullen E. (1995). *Mullen scales of early learning*. San Antonio, TX: Pearson.
- Noyes-Grosser DM, Elbaum B, Wu Y, Siegenthaler KM, Cavalari RS, Gillis JM, et al. (2018). Early intervention outcomes for toddlers with autism spectrum disorder and their families. *Infants and Young Children*, 31(3), 177–199.
- Postorino V, Fatta LM, De Peppo L, Giovagnoli G, Armando M, Vicari S, ... Mazzone L. (2015). Longitudinal comparison between male and female preschool children with autism spectrum disorder. *Journal of Autism and Developmental Disorders*, 7, 2046–2055.
- Reinhardt VP, Wetherby AM, Schatschneider C, & Lord C. (2015). Examination of sex differences in a large sample of young children with autism spectrum disorder and typical development. *Journal of Autism and Developmental Disorders*, 45(3), 697–706. [PubMed: 25189824]
- Rivet TT, & Matson JL (2011). Review of gender differences in core symptomatology in autism spectrum disorders. *Research in Autism Spectrum Disorders*, 5(3), 957–976.
- Rotholz DA, Kinsman AM, Lacy KK, & Charles J. (2017). Improving early identification and intervention for children with autism spectrum disorder. *Pediatrics*, 139, 1–7.
- Rutter MA, Bailey A, & Lord C. (2003). *The social communication questionnaire*. Los Angeles, CA: Western Psychological Services.
- Schendel D, DiGuseppi C, Croen L, Fallin D, Reed P, Schieve L, ... Yeargin-Allsopp M. (2012). The study to explore early development (SEED): A multi-site epidemiologic study of autism by the Centers for Autism and Developmental Disabilities Research and Epidemiology (CADDRE) network. *Journal of Autism and Developmental Disorders*, 42, 2121–2140. [PubMed: 22350336]
- Schuck RK, Flores RE, & Fung LK (2019). Brief report: Sex/gender differences in symptomatology and camouflaging in adults with autism spectrum disorder. *Journal of Autism and Developmental Disorders*, 49(6), 2597–2604. [PubMed: 30945091]
- Shattuck P, Durkin M, Maenner M, Newschaffer C, Mandell D, Wiggins L, Lee L-C, ... Cunniff C. (2009). Timing of identification among children with an autism spectrum disorder: Findings from

- a population-based surveillance study. *Journal of the American Academy of Child and Adolescent Psychiatry*, 48(5), 474–483. [PubMed: 19318992]
- Squires J, Bricker D, & Twombly E. (2015). *Ages & stages questionnaires®: Social-emotional. (ASQ®:SE-2): A parent-completed child monitoring system for social-emotional behaviors (second edition)*. Baltimore: Paul H. Brookes Publishing Co., Inc.
- Sullivan GM, & Feinn R. (2012). Using effect size – Or why the p value is not enough. *Journal of Graduate Medical Education*, 4(3), 279–282. [PubMed: 23997866]
- Sutherland R, Hodge A, Bruck S, Costly D, & Klieve H. (2017). Parent-reported differences between school-aged girls and boys on the autism spectrum. *Autism*, 21(6), 785–794. [PubMed: 28287270]
- Van Wijngaarden-Cremers PJM, van Eeten E, Groen WB, Van Deurzen PA, Oosterling IJ, & Van der Gaag RJ (2014). Gender and age differences in the core triad of impairments in autism spectrum disorders: A systematic review and meta-analysis. *Journal of Autism and Developmental Disorders*, 44(3), 627–635. [PubMed: 23989936]
- Wiggins LD, Bakeman R, Adamson LB, & Robins DL (2007). The utility of the Social Communication Questionnaire in screening for autism in children referred for early intervention. *Focus on Autism and Other Developmental Disabilities*, 22, 33–38.
- Wiggins LD, Reynolds A, Rice C, Moody EJ, Bernal P, Blaskey L, ... Levy S. (2015). Using standardized diagnostic instruments to classify children with autism in the Study to explore Early Development. *Journal of Autism and Developmental Disorders*, 45, 1271–1280. [PubMed: 25348175]

What this paper adds?

To examine sex-based differences in ASD phenotypes, we used a large and diverse community-based sample of preschool-aged children living in multiple geographic areas; standardized collection of behavioral, developmental, and diagnostic characteristics; and a comprehensive evaluation of children regardless of an existing ASD diagnosis. There were no meaningful sex differences in the outcomes assessed in our study. Sex-based variation in ASD phenotypes may emerge after the preschool years.

Author Manuscript

Author Manuscript

Author Manuscript

Author Manuscript

Table 1

Maternal and Site Characteristics of Preschool-Aged Children Evaluated for Autism Spectrum Disorder (ASD) by Study Group and Child Sex.

	Autism Spectrum Disorder			Subthreshold ASD Characteristics		
	<i>N</i> = 1480			<i>N</i> = 593		
	Males	Females	<i>X</i> ² (<i>p</i>)	Males	Females	<i>X</i> ² (<i>p</i>)
	<i>n</i> = 1209	<i>n</i> = 271		<i>n</i> = 416	<i>n</i> = 177	
<i>N</i> (%)	<i>N</i> (%)		<i>N</i> (%)	<i>N</i> (%)		
Maternal age			1.83 (0.839)			1.87 (0.834)
19 years or younger	1 (0.10)	0 (0.00)		0 (0.00)	0 (0.00)	
20– 29 years	127 (10.50)	21 (7.75)		92 (22.11)	42 (23.73)	
30– 34 years	304 (25.14)	70 (25.83)		105 (25.24)	43 (24.29)	
35– 39 years	415 (34.33)	95 (35.06)		112 (26.92)	51 (28.81)	
40 years or older	362 (29.94)	85 (31.48)		107 (25.72)	41 (23.16)	
Maternal education			2.51 (0.542)			3.20 (0.406)
Less than high school	47 (3.88)	16 (5.90)		51 (12.26)	20 (11.30)	
High school diploma	125 (10.34)	27 (9.96)		75 (18.03)	26 (14.69)	
Some college	379 (31.35)	88 (32.47)		134 (32.21)	70 (39.54)	
College/advanced degree	658 (54.42)	140 (51.66)		156 (37.50)	61 (34.46)	
Maternal race/ethnicity			1.09 (0.918)			0.79 (0.882)
Non-Hispanic White	684 (56.58)	162 (59.77)		203 (48.80)	88 (49.72)	
Non-Hispanic Black	278 (22.99)	62 (22.88)		135 (32.45)	56 (31.64)	
Hispanic	62 (5.13)	14 (5.17)		29 (6.97)	15 (8.47)	
Other	110 (9.10)	20 (7.38)		23 (5.53)	8 (4.52)	
Multi-race	49 (4.10)	11 (4.06)		22 (5.29)	8 (4.52)	
Missing	26 (2.15)	2 (0.74)		4 (1.00)	2 (1.13)	
Study site			1.57 (0.938)			9.06 (0.111)
California	188 (15.55)	47 (17.34)		41 (9.85)	17 (9.60)	
Colorado	227 (18.78)	48 (17.71)		65 (15.56)	23 (13.00)	
Georgia	238 (19.69)	47 (17.34)		106 (25.52)	32 (18.08)	
Maryland	204 (16.87)	50 (18.45)		28 (6.70)	20 (11.30)	
North Carolina	184 (15.22)	42 (15.50)		88 (21.21)	49 (27.68)	
Pennsylvania	168 (13.89)	37 (13.65)		88 (21.16)	36 (20.34)	

Table 2

Behavioral and Developmental Functioning Among Preschool-Aged Children Evaluated for Autism Spectrum Disorder (ASD) by Study Group and Child Sex.

	Autism Spectrum Disorder				Subthreshold ASD Characteristics			
	N = 1480		N = 593		Males		Femal	
	Males	Females	F (p)	η^2	Males	Femal	F (p)	η^2
	n = 1209	n = 271			n = 416	n = 177		
	Mean (SD)	Mean (SD)			Mean (SD)	Mean (SD)		
Child Behavior Checklist								
Externalizing t-score	59.62 (11.28)	60.44 (11.50)	3.58 (0.573)	0.003	59.11 (13.03)	57.44 (13.09)	2.02 (0.252)	0.001
Internalizing t-score	62.29 (9.63)	63.61 (9.82)	1.07 (0.334)	0.001	59.32 (11.90)	60.17 (11.91)	0.74 (0.424)	0.004
Mullen Scales of Early Learning								
Composite standard score	66.81 (19.76)	65.38 (18.74)	0.33 (0.609)	0.000	79.13 (18.38)	81.44 (19.77)	2.20 (0.112)	0.006
Fine motor t-score	29.75 (11.70)	28.81 (11.79)	1.02 (0.331)	0.001	37.78 (11.70)	39.82 (13.01)	3.56 (0.057)	0.002
Receptive language t-score	30.33 (13.00)	29.44 (12.47)	0.51 (0.492)	0.000	37.22 (12.90)	38.44 (12.92)	1.22 (0.278)	0.002
Expressive language t-score	29.33 (11.50)	28.52 (10.78)	0.51 (0.518)	0.000	36.43 (11.80)	38.06 (12.45)	2.60 (0.123)	0.004
Visual reception t-score	34.91 (15.46)	33.93 (15.14)	0.48 (0.504)	0.000	42.62 (12.43)	42.57 (13.72)	<.01 (0.901)	0.000

Note: An eta squared (η^2) estimate of at least 0.01 is needed to assume a small effect and an η^2 of at least 0.06 is needed to assume a moderate effect of child sex.

Table 3

Performance on an Autism Spectrum Disorder (ASD) Screen and Two ASD Diagnostic Tests Among Preschool-Aged Children Evaluated for ASD by Study Group and Child Sex.

	Autism Spectrum Disorder				Subthreshold ASD Characteristics			
	N = 1480		N = 593		Males		Females	
	Males	Females	F (p)	η^2	Males	Females	F (p)	η^2
	n = 1209	n = 271			n = 416	n = 177		
	Mean (SD)	Mean (SD)			Mean (SD)	Mean (SD)		
Social Communication Questionnaire								
Total score	17.35 (6.05)	17.82 (6.15)	1.39 (0.238)	.001	13.90 (5.25)	13.44 (4.69)	1.12 (0.290)	.002
Autism Diagnostic Interview-Revised (ADI- R)								
Restricted interests and repetitive behaviors raw score (RRB)	6.34 (2.50)	5.65 (2.58)	13.53 (<.010)	.009	3.67 (2.61)	3.21 (2.74)	3.72 (0.054)	.006
Social deficits raw score	18.38 (5.86)	19.11 (6.01)	3.16 (0.083)	.002	8.23 (5.95)	7.66 (5.47)	1.20 (0.267)	.002
Autism Diagnostic Observation Schedule								
RRB raw score	3.61 (1.69)	3.38 (1.79)	3.94 (0.052)	.003	1.51 (1.39)	1.29 (1.24)	3.27 (0.067)	.005
Social deficits raw score	8.86 (2.75)	8.92 (2.89)	0.10 (0.747)	.001	3.35 (2.74)	2.54 (2.41)	11.65 (<.010)	.019
Total calibrated severity score	7.18 (1.64)	7.16 (1.79)	0.03 (0.872)	.001	2.97 (2.19)	2.35 (1.71)	9.72 (<.010)	.019

Note: An eta squared (η^2) estimate of at least 0.01 is needed to assume a small effect and an η^2 of at least 0.06 is needed to assume a moderate effect of child sex.

Table 4

Parent-Reported Developmental Conditions Diagnosed by a Healthcare Provider among Preschool-Aged Children with Autism Spectrum Disorder by Child Sex.

	Autism Spectrum Disorder		<i>Benjamin-Hochberg Value (rank)</i>	χ^2 (p)	<i>Cramer's V</i>
	<i>N = 1480</i>				
	Males <i>n = 1209</i> <i>n (%)</i>	Females <i>n = 271</i> <i>n (%)</i>			
Autism spectrum disorder	1057 (87.43)	218 (80.44)	.006 (1)	9.43 (.009)	0.078
Any developmental condition	1177 (97.35)	255 (94.10)	.011 (2)	8.64 (.016)	0.082
Cerebral palsy	17 (1.41)	9 (3.32)	.017 (3)	4.67 (.138)	0.063
Language delay	807 (66.75)	173 (63.84)	.022 (4)	3.26 (.229)	0.054
Motor delay	184 (15.22)	52 (19.19)	.028 (5)	2.53 (.343)	0.039
Hearing problems	58 (4.79)	19 (7.01)	.033 (6)	2.22 (.344)	0.040
Vision problems	43 (3.56)	14 (5.17)	.038 (7)	1.52 (.483)	0.028
Down syndrome	5 (0.41)	2 (0.74)	.044 (8)	0.52 (.782)	0.022
Attention deficit hyperactivity disorder	87 (7.19)	17 (6.27)	.053 (9)	0.32 (.832)	0.013

Note: A *Cramer's V* estimates of at least 0.20 is needed to assume a small effect and a *Cramer's V* of at least 0.30 is needed to assume a moderate effect of child sex; the Benjamin-Hochberg value represents the significance threshold needed after correction.

Table 5

Parent-Reported Developmental Conditions Diagnosed by a Healthcare Provider among Preschool-Aged Children with Subthreshold Autism Spectrum Disorder (ASD) Characteristics by Child Sex.

Subthreshold ASD Characteristics					
<i>N</i> = 593					
	Males	Females			
	<i>n</i> = 416	<i>n</i> = 177			
	<i>n</i> (%)	<i>n</i> (%)	<i>Benjamin-Hochberg Value (rank)</i>	<i>X</i> ² (<i>p</i>)	<i>Cramer's V</i>
Autism spectrum disorder	190 (45.67)	60 (33.90)	.006 (1)	7.02 (.008)	0.10
Down syndrome	3 (0.72)	4 (2.26)	.011 (2)	2.55 (.126)	0.07
Attention deficit hyperactivity disorder	58 (13.94)	19 (10.73)	.017 (3)	1.54 (.192)	0.05
Hearing problems	32 (7.69)	19 (10.73)	.022 (4)	1.48 (.235)	0.04
Vision problems	8 (1.92)	1 (0.56)	.028 (5)	1.53 (.215)	0.03
Language delay	270 (64.90)	120 (67.80)	.038 (7)	0.63 (.442)	0.05
Motor delay	53 (12.74)	27 (15.25)	.033 (6)	0.73 (.427)	0.04
Cerebral palsy	8 (1.92)	4 (2.26)	.044 (8)	0.07 (.832)	0.01
Any developmental condition	359 (86.29)	154 (87.00)	.053 (9)	0.28 (.293)	0.01

Note: A *Cramer's V* estimates of at least 0.20 is needed to assume a small effect and a *Cramer's V* of at least 0.30 is needed to assume a moderate effect of child sex; the Benjamin-Hochberg value represents the significance threshold needed after correction.