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

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Abstract

This study examined the phenotypic profiles of children aged 30–68 months in the Study to Explore Early Development (SEED). Children classified as autism spectrum disorder (ASD), developmental delay (DD) with ASD symptoms, DD without ASD symptoms, and population comparison (POP) differed significantly from each other on cognitive, adaptive, behavioral, and

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social functioning and the presence of parent-reported conditions. Children with ASD and DD with ASD symptoms had mild to severe ASD risk on several measures compared to children with other DD and POP who had little ASD risk across measures. We conclude that children in SEED have varying degrees of ASD impairment and associated deficits. SEED thus provides a valuable sample to explore ASD phenotypes and inform risk factor analyses.

Keywords

Autism; Etiology; Symptoms; Phenotype; Study to Explore Early Development

Introduction

Autism spectrum disorder (ASD) is a developmental disorder defined by impairments in social interaction and communication and the presence of restricted interests and repetitive behaviors (RRB) (American Psychiatric Association 2013). The Centers for Disease Control and Prevention (CDC) currently estimates that an average of 1 in 68 children from multiple US communities has an ASD, a substantial increase from previous reports (CDC 2014). It is widely accepted that both genetic and non-genetic factors are associated with the development of ASD (Bailey et al. 1995; Hallmayer et al. 2011; Miles 2011), although distinct genetic mechanisms have been found for only 10–25 % of all children with an ASD (Abrahams and Geschwind 2008; Geschwind 2011; Miles 2011) and neither genetic nor non-genetic mechanisms are well understood. The search for ASD risk factors that could lead to preventive measures or treatment options has thus become a national research priority (Interagency Autism Coordinating Committee 2014).

One of the difficulties in ASD etiologic research arises from the substantial variability in ASD symptom severity and presentation, and in co-occurring behavioral, psychiatric, and medical conditions (Carlsson et al. 2013; Close et al. 2012; Levy et al. 2010). This phenotypic complexity is often apparent from the very early stages of development in children subsequently diagnosed with ASD. Most preschool children with ASD have more cognitive, adaptive, behavioral, and social delays than children with other developmental delays (DD) and typical development; although constellations of symptoms may vary among individual children. Severity gradients within the two diagnostic domains of social communication and RRB also range from mild to severe and do not always follow the same pattern across domains (e.g., some children may have severe social communication deficits and few RRB while other children may have mild social communication deficits and many RRB, Georgiades et al. 2013). Moreover, there is some indication that milder ASD symptoms extend beyond the classification of ASD, implicating a more dimensional than categorical developmental construct (Constantino 2011). Contrasting children with a range of ASD- and non ASD-related symptoms may thus provide insight into the causes of and treatments specific to ASD than considering only children with classic ASD symptomology.

The average age of earliest ASD diagnosis in the Unites States is 4.4 years (CDC 2014), which complicates research on the range of ASD phenotypes in early childhood. Consequently, screening children with an array of developmental conditions that often co-

occur with or are diagnosed before ASD is an ideal way to detect those with varying levels of ASD impairments. For instance, many preschool children with ASD may also have symptoms of attention deficit hyperactivity disorder (ADHD), intellectual disability (ID), language delays, and motor delays; (Carlsson et al. 2013); epilepsy and sensory integration disorder are commonly reported in older children with ASD (Levy et al. 2010; Peacock et al. 2012). Other children with ASD are not recognized with any DD until screened in a general pediatric setting (Miller et al. 2011). Few studies, however, have systematically screened for ASD in large samples of children, both with and without other DD, to ascertain ASD-related impairments and compare phenotypic profiles of children classified on the basis of a comprehensive developmental assessment. Although challenging to obtain, such an in-depth, standardized assessment of a large sample of children in multiple geographic areas would provide a valuable sample to explore various ASD phenotypes and inform risk factor analyses.

The Study to Explore Early Development (SEED) is a multi-site case–control study designed to explore possible risk factors for the development of ASD (Schendel et al. 2012; Wiggins et al. 2015). SEED presents a distinct opportunity to investigate a range of ASD phenotypes because of its large sample size, comprehensive data collection, and multiple comparison groups [i.e., ASD, DD, including DD with ASD symptoms, and population comparison (POP)]. Consequently, the goal of this paper is to compare the global phenotypic profile of children with ASD to the global phenotypic profile of children classified as DD with and without ASD symptoms and POP in SEED. We hypothesized that children with ASD would have more cognitive, adaptive, behavioral, and social deficits than other children in SEED; followed in order by children classified as DD with ASD symptoms, DD without ASD symptoms, and POP. We also hypothesized that children classified as DD with ASD symptoms would have more parent-reported ADHD, language delays, and motor delays than children classified as DD without ASD symptoms and POP. We intend this descriptive study as a first step in elucidating ASD phenotypes in children identified through SEED, thus setting the stage for future and more detailed analyses on individual symptoms and the link between phenotypes and etiologies.

Methods

Participant Ascertainment

SEED is a case–control study conducted in six study sites across the United States: California, Colorado, Georgia, Maryland, North Carolina, and Pennsylvania, and approved by Institutional Review Boards (IRB) at each site. Eligible children were born between September 1, 2003 and August 31, 2006 (30–68 months of age), resided in one of the six study catchment areas at birth and the time of first contact by SEED study staff, and lived with a knowledgeable caregiver who was competent to communicate orally in English (or in California and Colorado, in English or Spanish). A three-pronged strategy was designed to ascertain the SEED sample: (1) children in the POP group were identified from a random sample of birth certificates from state vital records, (2) children with potential ASD and DD were identified in each study area from multiple educational and health providers who diagnose and serve children with a range of developmental disabilities including ASD, and

(3) children with a potential ASD diagnosis were also referred by families or physicians. A detailed description of the SEED eligibility criteria, ascertainment methods, enrollment methods, and data collection protocol can be found in Schendel et al. (2012). Data from this analysis were collected in the original SEED protocol and did not require additional data collection or IRB approval.

ASD Screening and Study Data Collection Procedures

The Social Communication Questionnaire (SCQ; Rutter et al. 2003) was administered to screen for ASD. The SCQ score provided an initial quantification of the child's risk of ASD and identified whether the child would be tested for ASD, enabling more efficient use of study resources. The SCQ recommends a score of 15 points or greater as an indicator of risk for an ASD. However, based on past research that indicates an SCQ score of 11 maximizes sensitivity and specificity in young children, SEED investigators defined an SCQ score of 11 points or higher as an indicator of risk for an ASD (Allen et al. 2007; Lee et al. 2007; Wiggins et al. 2007). Analyses that support a SCQ cutoff score of 11 points in young children were subsequently replicated in the SEED sample (unpublished data).

Children with an SCQ score less than 11 points and without a previous ASD diagnosis were asked to complete a clinic visit consisting of administration of the Mullen Scales of Early Learning (MSEL) (Mullen 1995). If children scored a standard score of less than 78 standard points on the MSEL, the Vineland Adaptive Behavior Scales— Second Edition (VABS-II) (Sparrow et al. 2005) was also administered to the parent. Children and parents of children who obtained a score of 11 or higher on the SCQ or had a previous ASD diagnosis were asked to complete a more comprehensive developmental evaluation that consisted of the Autism Diagnostic Interview-Revised (ADI-R), Autism Diagnostic Observation Schedule (ADOS), MSEL, and VABS-II. These assessments were administered during one to three clinic visits by clinicians who had established research reliability. A small number of children who scored less than 11 points on the SCQ and did not have a previously documented ASD diagnosis were also administered the comprehensive evaluation if the study clinician suspected ASD during the clinic visit.

Additional information on phenotypic characteristics and ASD symptoms and behaviors was obtained via parent report on the Child Behavior Checklist (CBCL; Achenbach 1992), Social Responsiveness Scale (SRS; Constantino 2002), and a structured interview that collected information on demographics and a range of developmental, medical, and psychiatric conditions. Parents were provided with a preparation guide before the interview so they could collect information to reduce recall bias. The specific question used to assess developmental, medical, and psychiatric conditions was "Now I will ask you about some developmental information a doctor or health care provider may have told you about your child. Please note that a health care provider at the child's school such as a child psychologist, physical therapist, occupational therapist, or school nurse should also be considered a qualified health care professional in answering these questions; however, the child's teachers should not be considered health care providers. Has a doctor or health care provider ever told you that your child had or has any of the conditions in the preparation guide?" The interviewer would then read a list of conditions to the parent but did not

provide a definition of each condition for the parent. Therefore, these conditions represent parent-reported conditions that were presumably diagnosed any time before the interview but were not used to ascertain children for the study. Likewise, symptoms of these conditions may overlap with or reflect ASD symptoms in the child. See Table 1 and Table 2 for a list of study instruments used for this paper. All instruments collected in SEED are described in detail elsewhere (Schendel et al. 2012).

Final Study Classification

The SEED final classification algorithm was based on best practice guidelines, review of the literature, clinical experience, and a desire to create a uniform method of characterizing ASD symptoms in large cohorts of children. Final classifications were based on the results of the ADI-R and ADOS, with careful consideration of the child's overall developmental level. The SEED classification algorithm therefore considered ASD symptoms relevant to both the 4th and 5th editions of the diagnostic and statistical manual of mental disorders (American Psychiatric Association 1994,2013). Briefly, 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 (i.e., met criteria on the social domain and was within two points on the communication domain, met criteria on the communication domain and was within two points on the social domain, or met criteria on the social domain and had two points noted on the behavioral domain). Details on the SEED final classification algorithm can be found in Wiggins et al. (2015).

Children who did not meet SEED ASD criteria were initially classified into one of three additional final classification groups: (1) DD, (2) POP, and (3) Incomplete Classification. Children classified as DD were those identified in each study area from multiple educational and health providers who diagnose and serve children with a range of developmental disabilities including ASD. These children did not demonstrate ASD risk on the SCQ and/or did not meet the SEED ASD criteria. Children classified as DD were ascertained on the basis of having various developmental conditions possibly related to ASD, such as ADHD and language delay, among other diagnoses. These children were divided post hoc into two subgroups based on different ASD-specific symptom profiles. Children classified as DD with ASD symptoms were those who received a comprehensive developmental evaluation for ASD but did not meet the threshold for SEED ASD criteria. Children classified as DD without ASD symptoms were those who received a limited developmental evaluation because they did not have a previous ASD diagnosis noted in service records and scored below 11 points on the SCQ. Children classified as POP were those who were ascertained from birth records and received a limited developmental evaluation or received a comprehensive developmental evaluation but did not meet the SEED criteria for a final classification of ASD. Children classified as Incomplete Classification were those who were asked to complete a comprehensive developmental evaluation but did not complete the evaluation for any reason, and were thus excluded from these analyses.

Statistical Methods

Descriptive statistics were used to summarize the distribution of children in each SEED study group by child age, ethnicity, race, and sex. Omnibus Chi square analyses tested for

differences in child age, ethnicity, race, and sex and parent-reported conditions across all study groups; p values for these analyses show statistical differences for the omnibus test instead of statistical differences between individual study groups. Pairwise Chi square comparisons were conducted to show statistical differences between SEED study groups; pairwise Chi square analyses were corrected for multiple comparisons with the Bonferroni method. The Phi statistic (ϕ) is reported for these analyses to indicate the measure of association between binary variables.

Where sample size prevented stratification by child's race, sex, and study site, we report aggregate results on developmentally appropriate conditions noted in at least 1 % of our sample.

ANCOVA analyses were conducted to assess mean differences in cognitive, adaptive, behavioral, and social functioning and ASD symptom severity between study groups while controlling for the influence of child race, child sex, and study site. A Bonferonni correction was applied to ANCOVA analyses to account for multiple comparisons. Partial eta squared (η^2_p) is reported for these analyses to indicate the amount of variance in cognitive, adaptive, behavioral, and social functioning and ASD symptom severity accounted for by SEED final classification.

Results

A total of 3,769 index children were enrolled in SEED, 2,722 (72.2 %) attended a clinic visit, and 2,600 (68.9 %) completed enough of the clinic visit to be classified as ASD or non-ASD. The 122 children who attended a clinic visit but were not classified as ASD or non-ASD were excluded from the analyses due to incomplete or invalid data collection. The sample described in this paper is those 2,600 children who were classified as ASD or non-ASD (Fig. 1). Demographic information by ASD, DD, and POP study groups is presented in Table 3.

The SEED final classifications for the 2,600 children in these analyses were: ASD (n = 707), DD (n = 995), and POP (n = 898). Children with ASD were ascertained from community based service providers due to an ASD or other DD diagnosis (n = 697). Some children identified from birth certificate records also met study criteria for ASD (n = 10). Children classified as DD were ascertained from community based service providers due to an ASD or DD diagnosis (n = 995); children with a previous ASD diagnosis were retained in the DD group if they did not meet our study criteria for ASD. Children classified as POP were ascertained from birth certificate records (n = 898). As mentioned previously, the DD study group was divided into children with ASD symptoms (n = 305) and children without ASD symptoms (n = 690). There were no significant differences in any MSEL, CBCL, or SRS domain between DD children with ASD symptoms who did and did not meet criteria on at least one of the ADI-R or ADOS. In contrast, there were significant differences in almost all MSEL, CBCL, and SRS domains between DD children who (1) had ASD symptoms and did not meet at least one of the ADI-R or ADOS classification thresholds and (2) did not have ASD symptoms (the only exception being the MSEL fine motor domain). The definition of

children classified as DD with ASD symptoms thus remained children who received a comprehensive evaluation for ASD but did not meet SEED ASD criteria.

There were 1487 caregivers (53.4 %) who reported that a health care professional told them that their child had at least one behavioral, developmental, medical, and psychiatric condition other than ASD. There were differences in the frequencies of parent-reported conditions based on child race, child sex, and study site. However, we were unable to stratify our analyses on these variables due to the low frequencies of some conditions among study groups.

The most common conditions reported by parents of children with ASD were language delay (65.6 %), sensory integration disorder (27.9 %), and motor delay (19.5 %). Children with ASD had more parent-reported sensory integration disorder and vision problems than children in other study groups. Children classified as DD with ASD symptoms had more parent-reported ADHD than children in other study groups, and children classified as DD without ASD symptoms had more parent-reported Down syndrome than children in other study groups (Table 4). Children classified as ASD and those classified as DD with ASD symptoms had similar frequencies of parent-reported language delays, obsessive compulsive disorder (OCD), and self-injurious behaviors, and the prevalence of OCD and self-injurious behaviors in each of these two groups was higher than those reported among children classified as DD without ASD symptoms and POP (Table 4). Children in the POP group had the lowest prevalence of all parent-reported conditions.

Conditions not noted in at least 1 % of the sample and thus dropped from further analyses, included childhood schizophrenia (n = 0), Rett syndrome (n = 0), tuberous sclerosis (n = 1), childhood disintegrative disorder (n = 2), Tourette syndrome (n = 2), neurofibromatosis (n = 5), reactive attachment disorder (n = 6), bipolar disorder (n = 7), and Fragile × syndrome (n = 7).

Of the 2,600 children in these analyses, 99.1 % had MSEL early learning composite scores available, 99.4 % had SCQ scores available, 92.8 % had CBCL scores available, and 90.6 % had SRS scores available. Table 5 shows mean differences in cognitive, behavioral, and social functioning based on these measures while controlling for the influence of child race, child sex, and study site. There was a clear and progressive pattern demonstrating significant group differences in cognitive, behavioral, and social functioning even after controlling for covariates. Children with ASD showed the most deficits across measures, followed in order by children classified as DD with ASD symptoms, DD without ASD symptoms, and POP. There were significant differences in the mean performance of children classified as DD with ASD symptoms and DD without ASD symptoms across all MSEL, SCQ, SRS, and CBCL composite and domain scores.

Children classified as ASD or DD with ASD symptoms (n = 1012) completed an ADI-R and ADOS, and 99.3 % of these children completed at least one domain of the VABS-II. Table 6 shows differences in mean adaptive functioning and autism symptom scores between children with ASD and children with DD with ASD symptoms as a function of final classification. Children classified as ASD had more adaptive deficits than children classified

as DD with ASD symptoms. Children with ASD had more ASD-related symptoms as measured by the ADI-R than children classified as DD with ASD symptoms. Children with ASD also had a higher mean ADOS symptom severity score than children classified as DD with ASD symptoms (range 4–10 and M = 7, which translates as moderate symptom severity versus range 1–10 and M = 3, which translates as low symptoms severity, respectively).

Discussion

Our results confirm that children within the SEED sample have varying degrees of ASD symptoms and associated deficits. Children were delineated into four research groups based on ascertainment and clinical assessment: children with ASD had more cognitive, adaptive, behavioral, and social delays than other children in SEED, followed in order by children classified as DD with ASD symptoms, DD without ASD symptoms, and POP. Children classified as DD with ASD symptoms were significantly more impaired than children with other DD across all cognitive, behavioral, and social domains. Moreover, children classified as DD with ASD symptoms had mild ASD symptoms noted on both the ADOS and SRS compared to children with ASD who had moderate ASD symptoms noted on the ADOS and SRS (and children with other DD and POP who scored within the typical range on the SRS). These results support the idea that children classified as DD with ASD symptoms may represent a phenotype characterized by subthreshold ASD traits. These results also highlight the many needs of children with ASD symptoms and associated deficits and support future research to identify individual symptoms and risk factors that contribute to ASD symptom severity.

Many of the conditions reported on the caregiver interview comprise symptoms that overlap with ASD symptoms (e.g., ADHD, language delay, and sensory integration disorder) and may therefore represent different aspects of ASD phenotypes rather than distinct and co-occurring conditions. Nonetheless, it is important to highlight conditions that are reported frequently in children classified as ASD and DD with ASD symptoms so that future research can more thoughtfully examine individual symptoms that contribute to ASD phenotypes and their associated risks. Caregivers noted sensory integration disorder in 27.9 % of children with ASD, and this was the second most common condition reported in children with ASD and DD with ASD symptoms (after language delays). Previous research among similarly aged children suggests that more than 80 % of children with ASD have definite sensory integration problems when outcomes are based on the results of symptom questionnaires rather than probing about previously reported conditions (Tomchek and Dunn 2007). Future research should thus explore the role of sensory systems in the development and manifestation of ASD and interventions to address sensory concerns.

Children classified as DD with ASD symptoms were more similar to children with ASD than children with DD alone in terms of some parent-reported conditions. For instance, children classified as DD with ASD symptoms had similar frequencies of parent-reported language delays, OCD, and self-injurious behaviors as children with ASD, and the occurrences of parent-reported OCD and self-injurious behaviors were higher than those found in other study groups. Symptoms of OCD and self-injurious behaviors are common

among children with ASD and may be perceived by providers to be part of the ASD phenotype. Consequently, children classified as DD with ASD symptoms in SEED could represent an ASD trajectory defined by significant improvement (if previously diagnosed with ASD) or symptoms not fully expressed (if not previously diagnosed with ASD). Children with DD and ASD symptoms thus offer a unique opportunity to expand our understanding of diverse ASD profiles (Gerdts and Bernier 2011). Future studies using a general DD comparison group should consider the presence/absence of ASD features when defining children with DD in order to produce more phenotypic specificity. Future studies should also consider longitudinal analyses of children with various levels of ASD symptoms to elucidate different pathways of development.

Children classified as DD with ASD symptoms had more parent-reported ADHD (but not more parent-reported language or motor delays) than any other study group. Previous research shows that symptoms of ADHD occur in about 50 % of individuals with ASD, suggesting high phenotypic overlap and potential difficulty with differential diagnosis between these two conditions (Goldstein and Schwebach 2004; Sinzig et al. 2009). Etiologic risks implicated in both ADHD and ASD include genetic factors, maternal infection during pregnancy, maternal auto-immune disease, maternal psychotropic medication use, and pre-term birth (Taurines et al. 2012). Future research could examine overlapping symptoms between ADHD and ASD that contribute to symptom endorsement in both conditions or suggest common etiologic risks (Taurines et al. 2012; van der Meer et al. 2012). More comparative research is needed on specific phenotypic distinctions between ADHD and ASD and their influences on early development to guide etiologic research.

The POP comparison group was developmentally similar to what we would expect of children in the general population. Children classified as POP had a mean MSEL standard score of 102 and mean MSEL domain scores between 49 and 52, which represents average cognitive performance in this group (Table 1). Children classified as POP also showed few internalizing and externalizing behavior problems on the CBCL and few ASD symptoms on the SCQ and SRS. For most of the conditions reported in the caregiver interview, the prevalence among children in the POP group was comparable to estimates from other studies (Boyle et al. 2011; Law et al. 2000), supporting the conclusion that the POP group is phenotypically representative of the general population and thereby a valid general population comparison group for SEED etiologic analysis.

Parent-reported conditions among children in SEED were generally consistent with other reports of young children, although there were a few notable discrepancies. The rate of ADHD was lower among children classified as ASD (8.0 %), other DD (4.5 %), and POP (0.8 %) than expected given other analyses (Boyle et al. 2011; Levy et al. 2010; Simonoff et al. 2008; Visser et al. 2010). Additionally, the rate of epilepsy was lower among children classified as ASD (3.7 %) given other analyses (Tuchman et al. 2010; Viscidi et al. 2013). Both ADHD and epilepsy are more often diagnosed in older children than preschool children, so the young age of the SEED sample could explain the lower rates of ADHD and epilepsy reported in this paper. Finally, children classified as POP had a higher rate of undefined hearing problems (1.5 %) compared to other estimates (Boyle et al. 2011; Visser et al. 2010) derived from questions about moderate to profound hearing loss rather than a

hearing problem. Thus, the differences in reported hearing problems between SEED and other studies could be due to the framing of questions rather than unique characteristics of the SEED sample.

There are some limitations to our analysis that warrant discussion. First, parent-reported conditions were obtained via caregiver interview rather than by direct assessment of the child; site differences in the presence of parent-reported conditions could indicate state differences in the recognition or interpretation of developmental problems and the quality of services for those problems. There were also differences in parent-reported conditions based on child race and sex, although we were unable to stratify our analyses on these characteristics due to the low frequencies of some conditions among study groups. These analyses should therefore be interpreted with caution since results could vary depending on geographic region or race or sex of the child. Moreover, the racial and ethnic distribution of the sample was slightly different from other large-scale investigations in that the SEED sample comprised more White, Black, and multi-racial children and less Asian and Hispanic children. Sample demographics were expected to vary between SEED and other studies given different geographic locales and method of reporting child race and ethnicity versus maternal race and ethnicity (Walker et al. 2014).

Despite these limitations, our results suggest that SEED study groups represent children with varying degrees of ASD symptoms and associated deficits. Of particular importance was the identification of children with a range of ASD impairments that could help elucidate etiologic pathways of development. Children classified as ASD and DD with ASD symptoms are noteworthy in that they are more phenotypically similar to each other than children classified as other DD or POP (e.g., they have more cognitive, adaptive, behavioral, and social delays, and symptoms of OCD, self-injurious behaviors, and sensory integration problems than children classified as DD or POP). These data are important because they provide preliminary clues to pivotal symptoms that may help delineate ASD phenotypes and etiologies. Children with other DD and POP offer ideal comparison groups to explore ASD symptom specificity given few social communication concerns. We thus conclude that the SEED study groups offer an excellent opportunity to explore ASD phenotypes and inform future risk factor analyses.

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References

Abrahams BS, Geschwind DH. Advances in autism genetics: On the threshold of a new neurobiology. Nature Review Genetics. 2008; 9(5):341–355.

Achenbach, T. Child behavior checklist. Burlington, VT: Achenbach System of Empirically based Assessment; 1992.

Allen C, Silove N, Williams K, Hutchins P. Validity of the social communication questionnaire in assessing risk of autism in preschool children with developmental problems. Journal of Autism and Developmental Disorders. 2007; 37(7):1272–1278. [PubMed: 17080270]

American Psychiatric Association. Diagnostic and statistical manual of mental disorders. 4th ed.. Arlington, VA: American Psychiatric Publishing; 1994.

American Psychiatric Association. Diagnostic and statistical manual of mental disorders. 5th ed.. Arlington, VA: American Psychiatric Publishing; 2013.

Bailey A, Le Couteur A, Gottesman I, Bolton P, Simonoff P, Yuzda E, Rutter M. Autism as a strongly genetic disorder: Evidence from a British twin study. Psychological Medicine. 1995; 25(1):63–77. [PubMed: 7792363]

Boyle CA, Boulet S, Schieve LA, Cohen RA, Blumberg SJ, Yeargin-Allsopp M, et al. Trends in the prevalence of developmental disabilities in US children, 1997–2008. Pediatrics. 2011; 127:1034–1042. [PubMed: 21606152]

Carlsson LH, Norrelgen F, Kjellmer L, Westerlund J, Gillberg C, Fernell E. Coexisting disorders and problems in preschool children with autism spectrum disorder. The Scientific World Journal. 2013; 2013:1–6.

Centers for Disease Control and Prevention. Prevalence of autism spectrum disorders among children 8 years - autism and developmental disabilities monitoring network, 11 sites, United States, 2010. MMWR Surveillance Summaries. 2014; 63(SS02):1–21.

Close HA, Lee L-C, Kaufmann CN, Zimmerman AW. Co-occurring conditions and change in diagnosis in autism spectrum disorder. Pediatrics. 2012; 129:305–316.

Constantino, J. The social responsiveness scale. Los Angeles, CA: Western Psychological Services; 2002.

Constantino J. The quantitative nature of autistic social impairment. Pediatric Research. 2011; 69:55R–62R.

Department of Health and Human Services Interagency Autism Coordinating Committee. website: http://iacc.hhs.gov/strategic-plan/2013/index.shtml

Georgiades S, Szatmari P, Boyle M, Hanna S, Duku E, Zwaigenbaum L, et al. Investigating phenotypic heterogeneity in children with autism spectrum disorder: A factor mixture modeling approach. Journal of Child Psychology and Psychiatry. 2013; 54:206–215. [PubMed: 22862778]

Gerdts J, Bernier R. The broader autism phenotype and its implications on the etiology and treatment of autism spectrum disorders. Autism Research and Treatment. 2011; 2011:545901. Epub 2011 Aug 17. [PubMed: 22937250]

Geschwind DH. The genetics of autism spectrum disorders. Trends in Cognitive Science. 2011; 15(9): 409–416.

Goldstein S, Schwebach AJ. The comorbidity of pervasive developmental disorder and attention deficit hyperac-tivity disorder: Results of a retrospective chart review. Journal of Autism and Developmental Disorders. 2004; 34:329–339. [PubMed: 15264500]

Gotham K, Risi S, Pickles A, Lord C. The autism diagnostic observation schedule: Revised algorithms for improved diagnostic validity. Journal of Autism and Developmental Disorders. 2007; 37:613–627. [PubMed: 17180459]

Hallmayer J, Cleveland S, Torres A, Phillips J, Cohen B, Torigoe T, et al. Genetic heritability and shared environmental factors among twin pairs with autism. Archives of General Psychiatry. 2011; 68:1095–1102. [PubMed: 21727249]

Interagency Autism Coordinating Committee (IACC). IACC strategic plan for autism spectrum disorder (ASD) research— 2013 Update. 2014 April 2014. Retrieved from the US.

Law J, Boyle J, Harris F, Harkness A, Nye C. Prevalence and natural history of primary speech and language delay: Findings from a systematic review of the literature. International Journal of Language and Communication Disorders. 2000; 35(2):165–188. [PubMed: 10912250]

Lee L, David AB, Rusyniak J, Landa R, Newschaffer CJ. Performance of the social communication questionnaire in children receiving preschool special education services. Research in Autism Spectrum Disorders. 2007; 1:126–138.

Levy SE, Giarelli E, Lee LC, Schieve L, Kirby R, Cunniff C, et al. Autism spectrum disorder and co-occurring developmental, psychiatric, and medical conditions among children in multiple populations of the United States. Journal of Developmental and Behavioral Pediatrics. 2010; 31(4):267–275. [PubMed: 20431403]

Lord C, Risi S, Lambrecht L, Cook EH Jr, Leventhal BL, DiLavore PC, et al. the autism diagnostic observation schedule-generic: A standard measure of social and communication deficits associated with the spectrum of autism. Journal of Autism and Developmental Disorders. 2000; 30(3):205–223. [PubMed: 11055457]

Lord, C.; Rutter, M.; DiLavore, PC.; Risi, S. Autism diagnostic observation schedule. Los Angeles, CA: Western Psychological Services; 1999.

Lord C, Rutter M, Le Couteur AL. 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. 1994; 24(5):659–685. [PubMed: 7814313]

Miles JH. Autism spectrum disorders: A genetics review. Genetic Medicine. 2011; 13:278–294.

Miller JS, Gabrielsen T, Villalobos M, Alleman R, Wahmhoff M, Carbone PS, Sequra P. The each child study: Systematic screenign for autism spectrum disorders in a pediatric setting. Pediatrics. 2011; 127:866–871. [PubMed: 21482605]

Mullen, E. Mullen scales of early learning. San Antonio, TX: Pearson; 1995.

Peacock G, Djesika A, Lijing O, Grosse S. Autism spectrum disorders and health care expenditures: The role of co-occurring conditions. Journal of Developmental and Behavioral Pediatrics. 2012; 33:2–8. [PubMed: 22157409]

Rutter, MA.; Bailey, A.; Lord, C. The social communication questionnaire. Los Angeles, CA: Western Psycholgical Services; 2003.

Schendel D, DiGuiseppi C, Croen L, Fallin D, Reed P, Schieve L, et al. 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. 2012; 42:2121–2140. [PubMed: 22350336]

Simonoff E, Pickles A, Charman T, Chandler S, Loucas T, Baird G. Psychiatric disorders in children with autism spectrum disorders: Prevalence, comorbidity, and associated factors in a population-derived sample. Journal of the American Academy of Child and Adolescent Psychiatry. 2008; 47(921):929.

Sinzig J, Walter D, Doepfner M. Attention deficit/ hyperactivity disorder in children and adolescents with autism spectrum disorder: Symptom or syndrome? Journal of Attention Disorders. 2009; 13(2):117–126. [PubMed: 19380514]

Sparrow, S.; Balla, D.; Cicchetti, D. Vineland adaptive behavior scales. 2nd ed.. San Antonio, TX: Pearson; 2005.

Taurines R, Schwenck C, Westerwald E, Sachse M, Siniatchkin M, Freitag C. ADHD and autism: differential diagnosis or obverlapping traits? A selective review. Attention Deficit Hyperactivity Disorders. 2012; 4:115–139. [PubMed: 22851255]

Tomchek SD, Dunn W. Sensory processing in children with and without autism: A comparative study using the short sensory profile. American Journal of Occupational Therapy. 2007; 61:190–200. [PubMed: 17436841]

Tuchman R, Cucarro M, Alessandri M. Autism and epilepsy: Historical perspective. Brain and Development. 2010; 32(9):709–718. [PubMed: 20510557]

van der Meer JM, Oerlemans AM, van Steijn DJ, Lappenschaar MG, de Sonneville LM, Buitelaar JK, Rommelse NN. Are autism spectrum disorder and attention deficit hyperactivity disorder different manifestations of one overarching disorder? Cognitive and symptom evidence from a clinical and population-based sample. Journal of the American Academy of Child and Adolescent Psychiatry. 2012; 51:1160–1172. [PubMed: 23101742]

Viscidi EW, Triche EW, Pescosolido MF, McLean RL, Joseph RM, Spense SJ, Morrow EM. Clinical characteristics of children with autism spectrum disorder and co-occurring epilepsy. PLoS ONE. 2013; 8(7):e67797. [PubMed: 23861807]

Visser SN, Bitsko RH, Danielson ML, Perou R. Increasing prevalence of parent-reported attention deficit hyper-activity disorder among children—United States, 2003 and 2007. MMWR Surveillance Summaries. 2010; 59:1439–1443.

Walker CK, Krakowiak P, Baker A, Hansen R, Ozonoff S, Hertz-Picciotto I. Preecalmpsia, placental insufficiency, and autism spectrum disorder or developmental delay. JAMA Pediatrics. 2014 Advance on-line publication.

Wiggins LD, Bakeman R, Adamson LB, Robins DL. The utility of the social communication questionnaire in screening for autism in children referred for early intervention. Focus on Autism and Other Developmental Disabilities. 2007; 22:33–38.

Wiggins LD, Reynolds A, Rice C, Moody EJ, Bernal P, Blaskey L, et al. Using standardized diagnostic instruments to classify children with autism in the study to explore early development. Journal of Autism and Developmental Disorders. 2015; 45:1271–1280. [PubMed: 25348175]

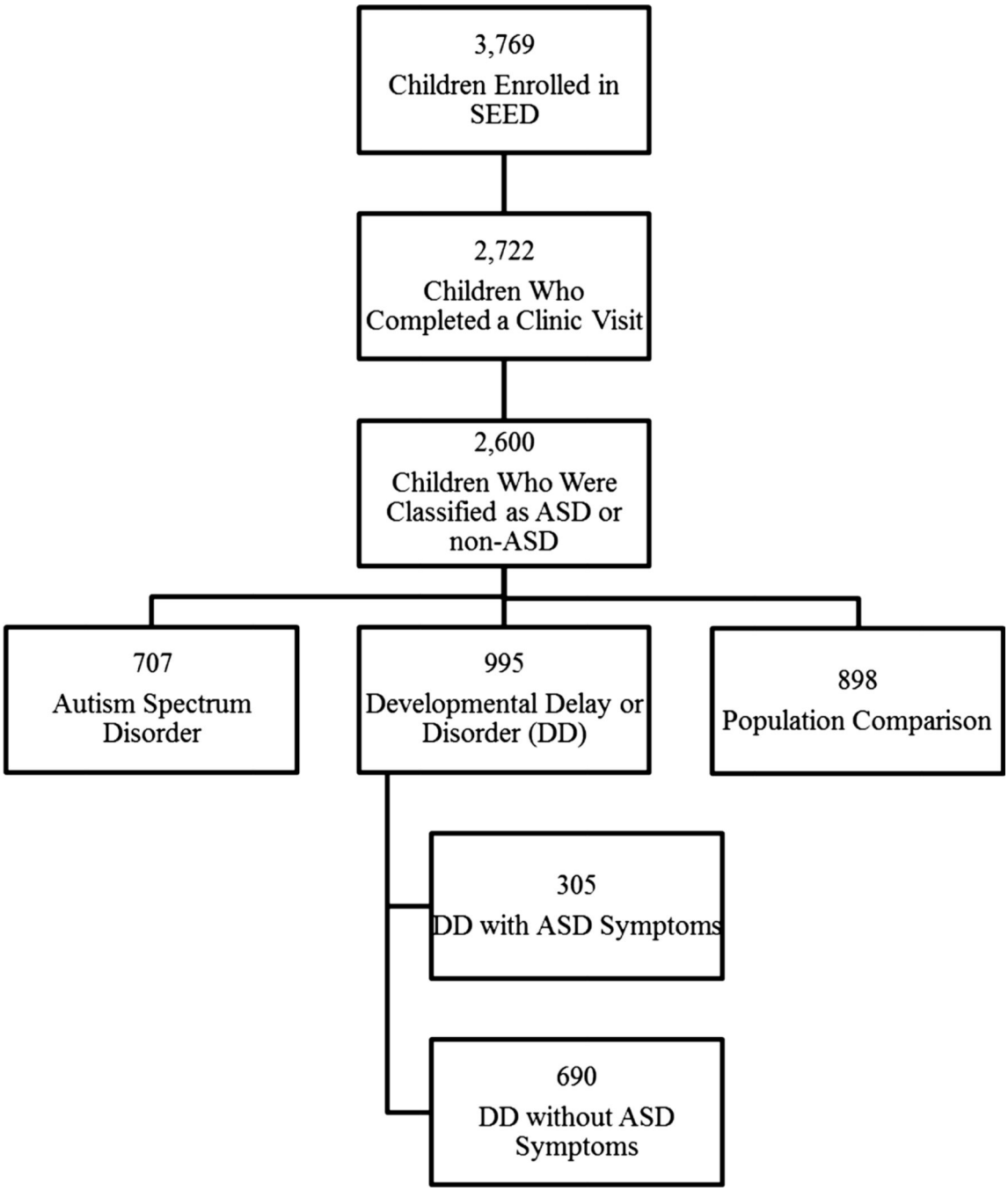

Fig. 1.
Participant selection criteria for the 2600 children described in these analyses

Table 1

Instruments administered to all participants in the Study to Explore Early Development

Data collection (reference)	Collection mode	Analytic variables	Scores[a]
Caregiver Interview (CGI; developed for SEED)	Telephone caregiver report	Child developmental, medical, and psychiatric conditions that the parent reported was endorsed by a health care provider any time prior to the interview	Presence of parent-reported condition recorded as yes or no
Child Behavior Checklist (CBCL; Achenbach 1992, 2000 ASBE Version)	Self-administered caregiver report	Internalizing and externalizing domains consisting of emotionally reactive, anxious/ depressed, somatic complaints, withdrawn, attention problems, and aggressive behavior	Domain t-scores with a score of 65 or more representing problem areas
Mullen Scales of Early Learning (Mullen 1995; 1995 AGS/ Pearson Version	Clinic assessment of child	Child age at time of developmental evaluation Early learning composite standard score and visual reception, fine motor, expressive language, and receptive language abilities	Age defined in months Early learning composite standard score with scores of 84 or less representing below average abilities Domain t-scores with scores of 39 or less representing below average abilities
Social Communication Questionnaire (SCQ; Rutter et al. 2003, 2003 WPS Current Version)	Telephone caregiver report	Social and communication deficits	Continuous total score with scores of 15 or more representing clinical risk and scores of 11 or more representing SEED risk
Social Responsiveness Scale (SRS; Constantino 2002; 2006 WPS Preschool and School-Aged Version)	Self-administered caregiver report	Severity of social deficit Receptive, expressive, cognitive, and motivational aspects of social behavior and ASD preoccupations	Total and domain t-scores with a scores of 60 or more representing problems areas

[a] Scores noted are the standard cutoff recommended by publishers unless otherwise noted (i.e., SCQ score of 11 indicated ASD risk whereas SCQ score of 15 indicates clinical risk)

Table 2

Instruments administered during the comprehensive developmental evaluation of children suspected to have an ASD in the Study to Explore Early Development

Data collection (reference)	Collection mode	Analytic variables	Scores
Autism Diagnostic Interview-Revised (ADI-R; Lord et al. 1994; 2003 WPS Version)	Clinic interview of caregiver	Final study classification	Autism cutoff scores are 10 for social deficits, 7–8 for communication deficits (depending on verbal abilities of the child), and 3 for behavioral deficits
Autism Diagnostic Observation Scale (ADOS; Lord et al. 1999, 2000; Gotham et al. 2007, 2001 WPS Version)	Clinic assessment of child	Final study classification and ASD symptom severity	Autism spectrum cutoff scores are dependent on age and/or language abilities of the child and range from 7 to 11; calibrated symptom severity score ranging from 1 to 10 with higher scores representing more severe symptoms
Vineland Adaptive Behavior Scales, Second Edition (VABS-II; Sparrow et al. 2005; AGS/Pearson Version)	Clinic interview of caregiver	Communication, daily living, socialization, and motor skills	Total and domain standard scores with scores of 85 or less representing deficit

Table 3

Differences in demographic information among children with and without ASD in the Study to Explore Early Development

	ASD M (SD)	DD M (SD)	POP M (SD)	F	*p*	η_P^2
Clinic visit age	**59.3 (6.70)[a]**	**59.6 (7.17)[a]**	**59.3 (7.39)[a]**	**0.28**	**.76**	**<.01**
	% (N)	**% (N)**	**% (N)**	**Omnibus χ^2**	***p***	**ϕ**
Gender–Male	82.0 (580)[a]	66.7 (664)[b]	53.1 (477)[c]	148.0	<.01	.24
Hispanic ethnicity	15.8 (112)[a]	17.1 (170)[a]	12.6 (113)[b]	7.74	.02	.05
Race-Asian	6.6 (47)[a]	3.5 (35)[b]	2.8 (25)[b]	16.4	<.01	.08
Race-Black	19.0 (134)[a]	17.5 (9174)[a]	11.8 (106)[b]	18.0	<.01	.08
Race-White	57.4 (406)[a]	62.6 (623)[b]	69.4 (623)[c]	25.0	<.01	.10
Race-Multiracial	12.2 (86)[a]	11.1 (110)[a]	12.0 (108)[a]	0.64	.73	.02
Race-Not stated	4.5 (32)[a]	4.9 (49)[a]	3.6 (32)[a]	2.18	.34	.03
Race-Other	0.3 (2)[a]	0.4 (4)[a]	0.4 (4)[a]	0.29	.87	.01

Different superscripts indicate significant differences in the distributions of individual study groups; analyses were corrected for multiple comparisons with the Bonferonni method

Table 4

Differences in parent-reported conditions among children with and without ASD in the Study to Explore Early Development (n = 2591 of 2600)

	ASD	DD with ASD symptoms	DD without ASD symptoms	POP			
	% (N)	% (N)	% (N)	% (N)	Omnibus χ^2	*p*	*p*
Any condition probed on the caregiver interview	80.5 (560)[a]	84.9 (259)[a,b]	76.3 (525)[c]	15.9 (143)[d]	977.5	<.01	.62
Attention deficit hyperactivity disorder	8.0 (56)[a]	14.1 (43)[b]	4.5 (31)[c]	0.8 (7)[d]	95.0	<.01	.19
Birth defect	5.2 (37)[a]	6.6 (20)[a,b]	8.0 (55)[b]	2.6 (23)[c]	24.5	<.01	.10
Cerebral palsy	2.3 (16)[a]	2.6 (8)[a]	2.3 (16)[a]	0.1 (1)[b]	19.2	<.01	.09
Down syndrome	1.0 (7)[a]	1.3 (4)[a]	5.1 (35)[b]	0.2 (2)[c]	55.7	<.01	.15
Epilepsy or seizure disorder	3.7 (26)[a]	3.9 (12)[a]	2.5 (17)[a]	0.1 (1)[b]	30.7	<.01	.11
Hearing problems	6.1 (43)[a]	6.9 (21)[a,b]	10.0 (69)[b]	1.4 (13)[c]	55.6	<.01	.15
Language delay	65.6 (458)[a]	64.3 (196)[a,b]	57.1 (394)[b]	8.9 (80)[c]	681.4	<.01	.51
Motor delay	19.5 (136)[a]	15.4 (47)[a,b]	14.2 (98)[b]	1.4 (13)[c]	144.0	<.01	.24
Obsessive compulsive disorder	3.0 (21)[a]	3.0 (9)[a]	0.3 (2)[b]	0.1 (1)[b]	38.5	<.01	.12
Self-injurious behaviors	5.6 (39)[a]	4.9 (15)[a]	0.7 (5)[b]	0.1 (1)[b]	69.2	<.01	.16
Sensory integration disorder	27.9 (195)[a]	16.1 (49)[b]	8.0 (55)[c]	0.9 (8)[d]	291.3	<.01	.34
Sleep problems	6.4 (45)[a]	3.9 (12)[a,b]	2.0 (14)[b]	0.6 (5)[c]	51.1	<.01	.14
Vision problems	4.7 (33)[a]	2.0 (6)[b]	3.2 (22)[b]	0.7 (6)[c]	27.3	<.01	.10

Note conditions are not mutually exclusive so several conditions could be reported for the same child; different superscripts indicate significant differences in the distributions of individual study groups; analyses were corrected for multiple comparisons with the Bonferonni method

Table 5

Differences in cognitive, behavioral, and social functioning among children with and without an ASD in the Study to Explore Early Development (n = 2600)

	ASD	DD with ASD symptoms	DD without ASD symptoms	POP				
	M	M	M	M	n	F	*p*	η_p^2
Mullen early learning composite standard score	66.9[a]	78.9[b]	89.5[c]	102.3[d]	2576	457.2	<.01	.35
Mullen visual reception t-score	34.5[a]	41.4[b]	46.4[c]	51.5[d]	2585	246.8	<.01	.22
Mullen fine motor t-score	30.2[a]	38.6[b]	42.3[c]	49.5[d]	2581	342.0	<.01	.28
Mullen receptive language t-score	30.5[a]	37.2[b]	44.5[c]	52.0[d]	2577	389.4	<.01	.31
Mullen expressive language t-score	29.2[a]	36.3[b]	43.1[c]	51.1[d]	2578	445.5	<.01	.34
CBCL internalizing problems t-score	62.5[a]	58.3[b]	47.8[c]	45.0[d]	2413	388.1	<.01	.33
Emotionally reactive t-score	61.1[a]	58.9[b]	53.5[c]	53.0[d]	2413	165.8	<.01	.17
Anxious/depressed t-score	56.1[a]	57.2[b]	52.5[c]	52.0[d]	2413	82.4	<.01	.10
Somatic complaints t-score	59.7[a]	58.4[b]	53.8[c]	52.9[d]	2413	150.4	<.01	.16
Withdrawn t-score	70.0[a]	62.3[b]	54.8[c]	53.1[d]	2413	618.7	<.01	.44
CBCL externalizing problems t-score	60.2[a]	56.9[b]	46.8[c]	43.9[d]	2413	296.0	<.01	.27
Attention problems t-score	63.4[a]	60.1[b]	54.3[c]	52.2[d]	2413	354.4	<.01	.31
Aggressive behaviors t-score	61.0[a]	58.9[b]	53.0[c]	52.1[d]	2413	156.0	<.01	.17
SCQ total score	17.4[a]	13.5[b]	4.9[c]	4.2[d]	2585	1389.9	<.01	.62
SRS total t-score	73.4[a]	63.6[b]	51.1[c]	47.6[d]	2358	1048.9	<.01	.57
SRS social awareness domain t-score	71.7[a]	62.1[b]	52.6[c]	50.6[d]	2358	596.3	<.01	.43
SRS social cognition domain t-score	71.5[a]	64.2[b]	51.2[c]	47.4[d]	2358	866.1	<.01	.52
SRS social communication domain t-score	72.3[a]	62.5[b]	50.8[c]	47.4[d]	2358	922.5	<.01	.54
SRS social motivation domain t-score	66.3[a]	58.4[b]	50.2[c]	47.8[d]	2358	448.4	<.01	.36
SRS autistic mannerisms domain t-score	72.1[a]	62.6[b]	50.9[c]	47.3[d]	2358	843.6	<.01	.52

Note that higher scores on the Mullen reflect more advanced abilities whereas higher scores on the SCQ, SRS, and CBCL reflect greater deficit; the number (n) of complete data collection points is out of the sample of 2,600 total children; different superscripts indicate significant mean differences between study groups; analyses were corrected for multiple comparisons with the Bonferonni method

Table 6

Differences in adaptive behavior and autism symptom severity among children who received a comprehensive developmental evaluation in the Study to Explore Early Development (n = 1012)

	ASD	DD with ASD symptoms				
	M	M	n	F	*p*	η_{P}^2
VABS adaptive behavior composite standard score	73.3	83.7	990	118.0	<.01	.11
VABS communication skills standard score	77.0	85.5	1005	53.4	<.01	.05
VABS daily living skills standard score	74.4	86.0	1005	123.3	<.01	.11
VABS socialization skills standard score	72.6	85.2	1003	186.0	<.01	.16
VABS motor skills standard score	80.2	87.8	1003	60.0	<.01	.06
ADI-R social deficits total score	18.3	7.7	1012	694.4	<.01	.41
ADI-R communication deficits total score	13.7	7.2	1012	540.9	<.01	.35
ADI-R behavioral deficits total score	6.0	3.3	1012	241.6	<.01	.19
ADOS severity score	7.2	3.0	1006	1232.6	<.01	.55

Higher scores on the VABS reflect more advanced abilities whereas higher scores on the ADOS reflect greater deficit; the number (n) of complete data collection points is out of the sample of 1012 children defined as ASD and DD with ASD symptoms