HHS Public Access

Author manuscript

J Autism Dev Disord. Author manuscript; available in PMC 2018 March 13.

Published in final edited form as:

J Autism Dev Disord. 2017 November ; 47(11): 3634–3645. doi:10.1007/s10803-017-3280-4.

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

Lisa D. Wiggins[1], **Lin H. Tian**[1], **Susan E. Levy**[2], **Catherine Rice**[3], **Li-Ching Lee**[4], **Laura Schieve**[1], **Juhi Pandey**[2], **Julie Daniels**[5], **Lisa Blaskey**[2], **Susan Hepburn**[6], **Rebecca Landa**[7], **Rebecca Edmondson-Pretzel**[8], and **William Thompson**[1]

[1]National Center on Birth Defects and Developmental Disabilities (NCBDDD), Centers for Disease Control and Prevention, 4770 Buford Highway MS E-86, Atlanta, GA, USA

[2]Center for Autism Research, Children's Hospital of Philadelphia, Philadelphia, PA, USA

[3]Emory Autism Resource Center, Emory University, Atlanta, GA, USA

[4]Department of Epidemiology, Johns Hopkins Bloomberg School of Public Health, Baltimore, MD, USA

[5]Department of Epidemiology, University of North Carolina, Chapel Hill, NC, USA

[6]JFK Partners, University of Colorado-Anschutz Medical Campus, Aurora, CO, USA

[7]Center for Autism and Related Disorders, Kennedy Krieger Institute, Baltimore, MD, USA

[8]Carolina Institute for Developmental Disabilities, University of North Carolina, Chapel Hill, NC, USA

Abstract

The objective of this study was to identify homogenous classes of young children with autism spectrum disorder (ASD) to improve phenotypic characterization. Children were enrolled in the Study to Explore Early Development between 2 and 5 years of age. 707 children were classified with ASD after a comprehensive evaluation with strict diagnostic algorithms. Four classes of children with ASD were identified from latent class analysis: *mild language delay with cognitive rigidity, mild language and motor delay with dysregulation, general developmental delay*, and *significant developmental delay with repetitive motor behaviors*. We conclude that a four-class phenotypic model of children with ASD best describes our data and improves phenotypic characterization of young children with ASD. Implications for screening, diagnosis, and research are discussed.

Correspondence to: Lisa D. Wiggins.

Author Contributions Study concept (LW), study design and methods (all authors), statistical plan (WT, LT, and LW), statistical analysis (LT), statistical review and interpretation (all authors), manuscript preparation and/or review (all authors).

Conflict of interest The authors do not have any conflicts of interest to report.

Keywords

Autism; Autism spectrum disorder; Characterization; Phenotypes; Subgroups

Introduction

Autism spectrum disorder (ASD) is a developmental disorder characterized by deficits in social communication and interaction and the presence of restricted interests and repetitive behaviors (RRB) (American Psychiatric Association 2013). Children with ASD present with remarkable heterogeneity in symptom presentation that ranges from severe impairments that require substantial supports to mild impairments that require fewer supports (APA 2013). The continuum of ASD-related challenges within the general population—and within families of individuals with ASD—supports a dimensional developmental construct defined by level of severity (Constantino 2011; Georgiades et al. 2013; Ring et al. 2008; Spiker et al. 2002; Wiggins et al. 2012). The ASD phenotype is further complicated by co-occurring behavioral, developmental, and medical conditions (Close et al. 2012; Levy et al. 2010). This phenotypic diversity complicates the search for ASD risk factors and effective screening, diagnosis, and treatment efforts.

Creating phenotypic subgroups of children with ASD may help elucidate the various etiologies that contribute to ASD symptomology. Creating phenotypic subgroups of children with ASD in the preschool years may also guide screening and diagnostic efforts and help define treatment selection and response. Consequently, numerous studies have attempted to partition children with ASD into meaningful subgroups based on ASD symptom profiles. The history of subtype analyses in ASD can generally be divided into diagnostic consensus and data generated techniques. In 1980, ASD, or Pervasive Developmental Disorders, were included as a “new” class of disorders in the Diagnostic and Statistical Manual of Mental Disorders-Third Edition (DSM-III, American Psychiatric Association 1980). Diagnostic criteria were modified and expanded in subsequent editions (American Psychiatric Association 1987, 1994, 2000, 2013). In DSM-IV-TR (2000), ASD was comprised of autistic disorder, Asperger disorder, childhood disintegrative disorder (CDD), Rett syndrome, and pervasive developmental disorder-not otherwise specified (PDD-NOS). In DSM-5, four of the aforementioned subtypes (excluding Rett syndrome) were combined into a singular condition with revised diagnostic criteria that may improve specificity, and thus enhance the ability to understand biological mechanisms and guide treatment choice. The changes introduced by the DSM-5 were largely driven by research data that showed (1) ASD is best described by two rather than three diagnostic domains, (2) subtype assignment is inconsistent across settings and over time, and (3) subtype assignment is a poor predictor of later outcome (Grzadzinski et al. 2013).

Data generated techniques utilize various aspects of the ASD phenotype to partition persons with ASD into meaningful subgroups. These techniques sort individuals into subtypes based on similarities in responses to observed data. Subtypes identified from data generated techniques are dependent on the observed data chosen for analysis. It is therefore prudent to consider which variables were used to identify ASD subtypes. Common variables used in

previous studies are ASD diagnostic symptoms, ASD symptom severity, adaptive functioning, cognitive functioning, and expressive language abilities (Frazier et al. 2012, 2008; Hu and Steinberg 2009; Rapin 1996; Sacco et al. 2012; Stevens et al. 2000; Wiggins et al. 2012). Using data generated techniques, previous studies have found between two and four subgroups of children with ASD, largely defined by level of ASD severity and cognitive functioning (Hu and Steinberg 2009; Rapin 1996; Sacco et al. 2012; Stevens et al. 2000; Wiggins et al. 2012). Other important subgroups found in previous research were defined by the DSM-5 diagnostic domains (i.e., social communication and interaction and restricted interests and stereotypes behaviors) and immune dysfunction (Frazier et al. 2012, 2008; Munson et al. 2008; Sacco et al. 2010; Snow et al. 2009).

One advantage of using data generated techniques to identify ASD subgroups is that a wide variety of diagnostic, behavioral, developmental, and medical data can be included in analytic models. However, many existing studies exclude co-occurring conditions that are common among persons with ASD and often influence developmental trajectory and treatment decisions. Moreover, some studies were limited to a single source of behavioral data obtained via parent interview and lacked adequate sample size, geographic variation, and/or in-depth evaluation of children with ASD. In fact, only a handful of studies have explored variables from multiple sources to create ASD subgroups. Therefore, the variables selection and data analysis techniques employed in previous studies lacked appreciation of the complex nature of ASD phenotypes and contribution of co-occurring conditions on developmental presentation.

The Study to Explore Early Development (SEED) is a multi-site case-control study designed to explore risk factors for the development of ASD (Schendel et al. 2012; Wiggins et al. 2015a, b). SEED presents a distinct opportunity to investigate ASD phenotypes because of its large sample size, comprehensive data collection, and thorough developmental assessment of child participants. The current study is an exploration of homogenous classes of children with ASD enrolled in SEED based on behavioral, developmental, and medical symptoms identified on a research assessment battery. We expected to find between two and four latent classes reflective of ASD symptom profiles that improve phenotypic characterization of young children with ASD in the preschool years.

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 at each site. Eligible children were born between September 1, 2003 and August 31, 2006, enrolled between 2 and 5 years of age, resided in one of the study areas, and lived with a knowledgeable caregiver who was competent to communicate in English (or in California and Colorado, in English or Spanish). Three groups of children were recruited from each site: (1) those with known ASD and (2) those with known developmental delays (DD) identified from multiple educational and health providers or family or physician referral, and (3) those from the general population identified from state vital records. The latter two groups were recruited in order to maximize the size of the final

ASD sample and provide two distinct comparison groups (i.e., children with DD but not ASD and children from the general population). Caregivers of enrolled children gave written consent to participate in the study. A detailed description of the SEED eligibility criteria, ascertainment methods, enrollment methods, and data collection procedures can be found in Schendel et al. (2012).

Data Collection Procedures

Children and families adhered to a common data collection protocol. The Social Communication Questionnaire (SCQ) (Rutter et al. 2003) was administered to all families to provide an initial assessment of ASD risk and determine assessment procedures. A SCQ score of 11 points or higher was chosen as an indicator of ASD risk, based on research that indicates a SCQ score of 11 maximizes sensitivity and specificity in young children (Allen et al. 2007; Lee et al. 2007; Wiggins et al. 2007). Families of children who obtained a score of 11 or higher on the SCQ, had a previous ASD diagnosis, or demonstrated ASD behaviors during the clinic visit were asked to complete the autism diagnostic interview-revised (ADI-R) (Lord et al. 1994), autism diagnostic observation schedule (ADOS) (Gotham et al. 2007; Lord et al. 2000, 1999), Mullen scales of early learning (MSEL) (Mullen 1995), and Vineland adaptive behavior scales-second edition (VABS-II) (Sparrow et al. 2005). The MSEL was used to assess expressive language, fine motor, receptive language, and visual reception skills. All other families of children who did not demonstrate ASD risk were asked to complete the MSEL (and the VABS-II if the child scored less than 78 standard points on the MSEL), but not the ADI-R or ADOS.

Additional information on phenotypic characteristics and ASD symptoms was obtained via the child's birth certificate and parent report on the child behavior checklist (CBCL) (Achenbach 1992), child sleep habits questionnaire (CSHQ) (Owens et al. 2000), early development questionnaire (EDQ) (Ozonoff et al. 2005), gastrointestinal questionnaire (GIQ) (created for SEED) (Schendel et al. 2012), and a structured interview that collected information on demographics and a range of co-occurring conditions previously diagnosed by a healthcare provider (Maternal Interview).

ASD Case Status

A total of 1012 families completed a comprehensive developmental evaluation that included the ADI-R (a comprehensive parent interview) and ADOS (a direct assessment of the child), and 707 met the SEED criteria for ASD. The SEED ASD case status 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. ASD case status was based on the results of gold-standard ASD diagnostic instruments rather than previous diagnosis. Briefly, children classified as ASD were those who met ASD criteria on both the ADI-R and the ADOS 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. (2015b). It is important to note that ADOS-2 algorithms were utilized in SEED in order to correspond with the DSM-5 definition of ASD.

Variable Identification

All children included in the analysis were expected to have social-communication deficits since they were classified with ASD using strict diagnostic algorithms. Therefore, global measures of social communication were included (i.e., the social communication questionnaire total score and the ADOS severity score) instead of a multitude of specific symptoms (e.g., deficits in eye contact) so that other variables that distinguish children ASD could be identified. Other items for the analyses were selected using a multistage procedure. First, a literature review was conducted to identify studies that classified children with ASD into subgroups. We specifically focused on studies that distinguished children with ASD from each other rather than children with ASD from children without ASD. A list of variables used in previous studies was compiled for review and discussion. Second, members of the author group—who have a broad range of expertise in epidemiology, pediatrics, and psychology—reviewed variables used in previous studies and discussed additional aspects of ASD phenotypes that could differentiate children with ASD. For instance, internalizing and externalizing behavior problems are typically excluded from ASD subgroup analyses or measured on a dichotomous or limited ordinal scale. Members of the author group felt these behaviors were important aspects of the ASD phenotype that could influence treatment choice and response. We therefore included t-scores that measured aggressive behaviors, anxiety/depression, attention problems, emotional reactivity, somatic complaints, and withdrawn behaviors in the LCA model. Third, potential items were reviewed to assess their availability in the SEED dataset. Based on this process, 27 items were selected for the analysis (Table 1).

VABS-II standard scores were excluded from the LCA because of the correlation with MSEL standard scores. However, mean VABS-II standard scores will be reported for each latent class. MSEL age equivalents were chosen for the LCA model due to floor-effects on some MSEL domain scores; both MSEL t-scores and age equivalents will be reported for each latent class.

Statistical Methods

Latent class analysis (LCA) was used to identify subgroups of children with ASD. LCA assumes that responses on observed variables can be explained by membership in unmeasured latent classes. Individuals are classified into subgroups based on similar patterns of observed data that reflect probability of class membership. LCA allows covariates to predict latent class membership and mixed types of observed variables (e.g., categorical and continuous variables) can be included simultaneously in an extended LCA model.

First, we assessed the best fit for a series of potential models using the following selection criteria: Bayesian information criterion (BIC), sample adjusted BIC (SABIC), and Lo-Mende–Rubin likelihood ratio test (LMR-LRT) (Nylund et al. 2007). Lower BIC or lower SABIC values indicate improved model fit. A statistically significant LMR-LRT *p*-value

indicates better fit than the model with one fewer class. Entropy ranged from 0 to 1, where higher entropy indicates greater precision in classification.

Second, to improve model parsimony and estimation, we excluded items where the response probabilities were close to 0.5 or where the relative mean differences across latent classes were less than 1% (Wurpts and Geiser 2014). We deemed these items “low quality” since response probabilities close to 0.5 and relative mean differences less than 1% indicate the items do not distinguish latent classes. We refit the previously tested models and selected the best model according to BIC, SABIC, and LMR-LRT. Results are presented for the final model after low quality items were dropped from the analyses.

Third, we examined a series of covariates that might theoretically predict latent class membership: child age, child ethnicity, child race, child sex, maternal education, primary language, and SEED site using the improved 3-step method to account for classification error (Asparouhov and Muthén 2013; Vermunt 2010). Model parameters were estimated using maximum likelihood with robust standard errors, which is an adjustment approach to dealing with non-normal data. All latent class modeling was executed using Mplus version 7 (Muthén and Muthén 2015).

Results

Initially, using the sample of 707 children with ASD from SEED, the best fitting model was a four-class model. Gestational age and history of child gastrointestinal symptoms were identified as low quality items and subsequently dropped from analyses. Table 2 shows model fit indices for the 25 remaining LCA variables. The four-class and five-class models had lower BIC and SABIC values than one, two, or three-class models. The LMR-LRT test supported the four-class model ($p = 0.001$), as the five-class model did not provide significantly better fit than the four-class model ($p = 0.567$). Entropy values for all the models were greater than 0.90 indicating high precision of latent classifications.

Item response probabilities and means for each item by latent class are shown in Table 3. A summary of between-class differences for each item is outlined in Table 4. Class 1 represented 28% of the sample. Children in this class were least impaired in terms of cognitive functioning, particularly nonverbal cognitive ability; average MSEL domain T scores (mean = 50; standard deviation = 10) and age equivalents were 39.36 and 50.62 for expressive language (EL), 44.26 and 56.97 for receptive language (RL), 42.04 and 54.64 for fine motor (FM), and 49.58 and 61.22 for visual reception (VR), respectively. Children in Class 1 had an average VABS-II composite score of 86.42 points. These children had the youngest age of single word development and were less likely to experience developmental regression than children in other classes. However, children in this class had high rates of restricted interests and unusual sensory responses.

Class 2 represented 26% of the sample. Children in this class were most impaired in terms of cognitive functioning; average MSEL domain T scores and age equivalents were 20.12 and 14.43 for EL, 20.17 and 15.18 for RL, 20.18 and 23.02 for FM, and 20.23 and 23.10 for VR, respectively. The average VABS-II composite score for children in Class 2 was 57.48 points.

Children in this class acquired single words at older ages (if at all) and were latest to walk unsupported. They also showed more repetitive motor mannerisms relative to children in other classes. Children in this class were at greatest risk of seizures and showed high rates of unusual sensory responses.

Class 3 represented 34% of the sample. Children in this class showed significant impairments in cognitive functioning; average MSEL domain T scores and age equivalents were 25.29 and 34.02 for EL, 24.68 and 34.17 for RL, 25.27 and 37.35 for FM, and 29.96 and 40.43 for VR, respectively. The average VABS-II composite score for children in Class 3 was 73.67 points. Children in this class were similar to children in Class 1 on most other variables, except for increased parental reports of developmental regression and higher overall autism symptom severity. Children in Class 3 also were identified more often as having later single word development than children in Class 1. Similar to other classes, children in Class 3 had a high rates of unusual sensory responses.

Class 4 represented 12% of the sample. Children in this class had average nonverbal functioning and mild language and motor delays; average MSEL domain T scores and age equivalents were 36.13 and 46.29 for EL, 36.41 and 48.21 for RL, 38.03 and 49.98 for FM, and 42.90 and 53.79 for VR. Children in Class 4 had an average VABS-II composite score of 75.95 points. Children in this class had increased cognitive rigidity, and relatively higher rates of aggressive behaviors, anxiety/depression, attention problems, emotional reactivity, self-injurious behaviors, sleep problems, and somatic complaints than children in other classes. Children in this class were more delayed in their use of a shared social smile than children in the other classes. Children in Class 4 also showed high rates of unusual sensory responses.

Sample characteristics are summarized in Table 5 and covariate associations with latent classes are summarized in Table 6. Children in Class 2 (i.e., those with the most significant cognitive impairments) were chosen as the reference category. Child age, child race, maternal education, and SEED site were significant predictors of latent class membership. Specifically, older children were more likely to be members of Class 1 or Class 4 relative to Class 2. Black children were less likely to be members of Class 1 relative to Class 2. Mothers with a college education or higher were more likely to have children placed in Class 1 or Class 3 relative to Class 2. Children enrolled in the GA site were less likely to be placed in Class 1 as compared to Class 2.

Discussion

We identified four classes of children with ASD. Children in Class 1 (28%) are best described as *mild language delay with cognitive rigidity*. These children had average cognitive functioning, mild impairments in language, and increased cognitive rigidity. Children in Class 2 (26%) are best described as *significant developmental delay with repetitive motor behaviors*. These children had well below average cognitive functioning, early emerging verbal and motor delays, and prominent repetitive motor mannerisms. Children in Class 3 (34%) are best described as *general developmental delay*. These children had well below average cognitive functioning and high-moderate autism symptom severity.

Children in Class 4 (12%) are best described as *mild language and motor delay with dysregulation*; these children had average nonverbal functioning, mild impairments in language and motor skills, increased cognitive rigidity, and high rates of problem behaviors. All children had high rates of unusual sensory response.

The four-class model of ASD described herein is a first step in understanding how symptoms associated with ASD cluster together in the preschool years when ASD is often first recognized. These symptom profiles can be used to guide screening and diagnostic efforts and inform future studies on etiology and developmental trajectory. For instance, language delays are often the first concern noted by parents of children with ASD (Kozlowski et al. 2011). However, two classes of children with ASD in our sample had only mild language delays coupled with cognitive rigidity and unusual sensory response (i.e., *mild language delay with cognitive rigidity* and *mild language and motor delay with dysregulation*). It is therefore important for healthcare providers to assess cognitive rigidity and unusual sensory response in screening and diagnostic practices for children with near typical language development. Moreover, children classified as *significant developmental delay with repetitive motor behaviors* had early emerging verbal and motor delays, significant cognitive delays, and prominent repetitive motor mannerisms. Compared to children in other latent classes, children classified as *significant developmental delay with repetitive motor behaviors* were latest to talk in single words (M = 30 months) and walk unsupported (M = 16 months), suggesting developmental differences within the first few years of life that may trigger deviances in subsequent maturation (Viding and Blakemore 2007). Children who are late to talk and walk may therefore need additional screening for ASD and increased monitoring of cognitive and behavioral development.

Our results can also be used to inform future studies on ASD etiologies and treatment selection. Children with *mild language and motor delay with dysregulation* had average nonverbal problem solving skills and mild impairments in language and motor functioning. These children also had many behavior problems and sleep dysregulation, which may indicate unique etiologies and service needs (McGuire et al. 2016). Circadian dysfunction has been linked to language delays in children with ASD (Hu et al. 2009) although no identified studies have linked circadian dysfunction, self-injurious behaviors, and behavior problems in children with ASD. More in-depth investigation of prominent *mild language and motor delay with dysregulation* symptoms could help elucidate etiologic pathways and other phenotypic manifestations of this ASD profile. Diagnostic qualifiers and longitudinal studies that focus on behavior and sleep dysregulation would encourage detailed monitoring of *mild language and motor delay with dysregulation* symptoms and their association with current functioning and future behavioral and emotional health.

It is interesting to note that unusual sensory responses were frequently reported for children in each latent class (i.e., item response probabilities between 0.91 and 0.97). DSM-5 includes unusual sensory responses as a criterion for diagnosis for ASD because these responses are common among children with ASD and tend to distinguish children with ASD from children with other developmental disorders. Our finding further demonstrates the impact of sensory dysregulation on children with ASD, highlights the importance of sensory

interventions, and supports the DSM revision of ASD diagnostic criteria to include sensory reactivity.

DSM-5 revisions to the conceptualization of ASD imply a dimensional approach to the disorder that captures variability within diagnostic and developmental domains. Our findings support a dimensional model of ASD in patterns of verbal and nonverbal abilities and autism symptom severity: these variables were similarly distributed in that children with *mild language delay with cognitive rigidity* were least impaired, followed by children with *mild language and motor delay with dysregulation, general developmental delay*, and *significant developmental delay with repetitive motor behaviors*, respectively. However, a four-class model of ASD was also supported when co-occurring behavioral, developmental, and medical conditions were considered. This four-class model of ASD highlights the influence of co-occurring conditions on phenotypic presentation and suggests that the presence of these conditions *within* the autism spectrum may be a better indicator of shared etiology and brain dysfunction (Lai et al. 2013; Waterhouse and Gillberg 2014). Adding diagnostic qualifiers that encompass common co-occurring conditions to the definition of ASD may therefore increase the likelihood of identifying ASD subgroups comprised of children with common risk factors and response to treatment. More fine-grained analyses of these latent classes are needed to facilitate research and precision treatments. Longitudinal follow-up studies are especially warranted to investigate the association between class membership and future outcomes.

There were several limitations associated with these analyses. The results of LCA are dependent on the variables used to generate latent classes and characteristics of the sample. Replication studies are needed to demonstrate the stability of our subgroups in other samples of children; longitudinal studies are needed to examine the trajectory of subgroups over time. The young age of the SEED population limited exploration of latent classes across age groups. Most of our latent class variables were obtained via parent report, which could have been subject to recall bias. Moreover, some covariates were significant predictors of latent class membership, which could indicate selective case participation. It is not surprising that older children were less likely to show cognitive impairment, since older children have more opportunities for cognitive growth and time to respond to interventions. Black children and children in GA were less likely to be *mild language delay with cognitive rigidity* than *significant developmental delay with repetitive motor behaviors*; these findings could be attributed to the observed association among Black children with ASD and cognitive impairment (Autism and Developmental Disabilities Monitoring Network Surveillance Year 2010 Principal Investigators 2014) and more Black children enrolled in GA than other sites. Mothers with a college education were more likely to have children with *mild language delay with cognitive rigidity* or *general developmental delay* than *significant developmental delay with repetitive motor behaviors*, which could be a consequence of more access to services and better quality health care. Other related sociodemographic factors could have had similar effects. Future studies could further explore the independent effects of other sociodemographic factors such as household income, financial insecurity, and neighborhood characteristics.

Despite these limitations, we believe ours is the most comprehensive study of ASD phenotypes to date. We utilized a large sample of children with ASD from multiple geographic locations. The classification of ASD was based on multi-dimensional standardized assessment. Variables were chosen from child observation and parent report measures. Additionally, the analytic approach employed in this study was based on model fit and parsimony, and allowed consideration of variables that influence latent class membership. Our model generated an entropy value of 0.92; the high precision in latent classification increases confidence in latent class assignment. We therefore conclude that a fourclass phenotypic model of children with ASD that considers co-occurring conditions best describes our data, improves characterization of young children, supports screening and diagnostic efforts, and informs future studies on etiology and developmental trajectory. SEED is well positioned to investigate the association between different ASD risk factors and phenotypes and plans to build upon these analyses in future studies.

Acknowledgments

We would like to thank the children and families who participated in this research. This publication was supported by six cooperative agreements from the Centers for Disease Control and Prevention: 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. 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. 3. Washington, DC: American Psychiatric Association; 1980.

American Psychiatric Association. Diagnostic and statistical manual of mental disorders. 3. Washington, DC: American Psychiatric Association; 1987. rev

American Psychiatric Association. Diagnostic and statistical manual of mental disorders. 4. Washington, DC: American Psychiatric Association; 1994.

American Psychiatric Association. Diagnostic and statistical manual of mental disorders. 4. Washington, DC: American Psychiatric Association; 2000. text rev

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

Asparouhov, T., Muthén, B. [Accessed on January 22, 2016] Auxiliary variables in mixture modeling: 3-Step approaches using Mplus. 2013. from http://www.statmodel.com/examples/webnotes/webnote15.pdf

Autism and Developmental Disabilities Monitoring Network Surveillance Year 2010 Principal Investigators. Prevalence of autism spectrum disorder among children aged 8 years—Autism and developmental disabilities monitoring network, 11 sites, United States, 2010. Morbidity and Mortality Weekly Report Surveillance Summaries. 2014; 63(SS02):1–21.

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

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

Frazier TW, Youngstrom EA, Kuba CS, Sinclair L, Rezai A. Exploratory and confirmatory factor analysis of the autism diagnostic interview—Revised. Journal of Autism and Developmental Disorders. 2008; 38:474–480. [PubMed: 17619129]

Frazier TW, Youngstron EA, Speer L, Embacher R, Law P, Constantino J, et al. Validation of proposed DSM-5 criteria for autism spectrum disorder. Journal of the American Academy of Child and Adolescent Psychiatry. 2012; 51(1):28–40. [PubMed: 22176937]

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]

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]

Grzadzinski R, Huerta M, Lord C. DSM-5 and autism spectrum disorders (ASDs): An opportunity for identifying ASD subtypes. Molecular Autism. 2013; 4:1–6. [PubMed: 23311570]

Hu VW, Sarachana T, Kim KS, Nguyen A, Kulkarni S, Steinberg ME, et al. Gene expression profiling differentiates autism case-controls and phenotypic variants of autism spectrum disorders: Evidence for circadian rhythm dysfunction in severe autism. Autism Research. 2009; 2:78–97. [PubMed: 19418574]

Hu VW, Steinberg ME. Novel clustering of items from the autism diagnostic interview – revised to define phenotypes within autism spectrum disorders. Autism Research. 2009; 2:67–77. [PubMed: 19455643]

Kozlowski AM, Matson JL, Horovitz M, Worley JA, Neal D. Parents' first concerns of their child's development in toddlers with autism spectrum disorder. Developmental Neurorehabilitation. 2011; 14(2):72–78. [PubMed: 21410398]

Lai M-C, Lombardo MV, Chakrabarti B, Baron-Cohen S. Subgrouping the autism "spectrum": Reflections on DSM-5. PLoS Biology. 2013; 11(4):e1001544.doi: 10.1371/journal.pbio.1001544 [PubMed: 23630456]

Lee L-C, 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, 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; 30:205–223. [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; 24:659–685. [PubMed: 7814313]

McGuire K, Fung LK, Hagopian L, Vasa RA, Mahajan R, Bernal P, et al. Irritability and problem behavior in autism spectrum disorder: A practice pathway for pediatric primary care. Pediatrics. 2016; 137:S136–S148. [PubMed: 26908469]

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

Munson J, Dawson G, Sterling L, Beauchaine T, Zhou A, Koehler E, et al. Evidence for latent classes of IQ in young children with autism spectrum disorder. American Journal of Mental Retardation. 2008; 113:439–452. [PubMed: 19127655]

Muthén, LK., Muthén, BO. Mplus user's guide. 7. Los Angeles, CA: Publishing; 2015.

Nylund KL, Asparouhov T, Muthén B. Deciding on the number of classes in latent class analysis and growth mixture modeling: A Monte Carlo Simulation Study. SEM: A Multidisciplinary Journal. 2007; 14:535–569.

Owens JA, Spirito A, McGuinn M. The children's sleep habits questionnaire (CSHQ): Psychometric properties of a survey instrument for school-aged children. Sleep. 2000; 23(8):1043–1051. [PubMed: 11145319]

Ozonoff S, Williams BJ, Landa R. Parental report of the early development of children with regressive autism: The delaysplus regression phenotype. Autism: The International Journal of Research and Practice. 2005; 9:461–486. [PubMed: 16287700]

Rapin, I., editor. Preschool children with inadequate communication. New Jersey: Mac Keith Press; 1996.

Ring H, Woodbury-Smith M, Watson P, Wheelwright S, Baron-Cohen S. Clinical heterogeneity among people with high functioning autism spectrum conditions: Evidence favouring a continuous severity gradient. Behavior and Brain Functioning. 2008; 4(11):1–6.

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

Sacco R, Curatolo P, Manzi B, Militerni R, Bravaccio C, Frolli A, et al. Principal pathogenetic components and biological endophenotypes in autism spectrum disorders. Autism Research. 2010; 3:237–252. [PubMed: 20878720]

Sacco R, Lenti C, Saccani M, Curatolo P, Manzi B, Bravaccio C, et al. Cluster analysis of autistic patients based on principal pathogenetic components. Autism Research. 2012; 5:137–147. [PubMed: 22431251]

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]

Snow AV, Lecavalier L, Houts C. The structure of the Autism diagnostic interview—Revised: Diagnostic and phenotypic implications. Journal of Child Psychology and Psychiatry. 2009; 50(6): 734–742. [PubMed: 19207624]

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

Spiker D, Lotspeich IJ, Dimiceli S, Myers RM, Risch N. Behavioral phenotypic variation in autism multiplex families: Evidence for a continuous severity gradient. Journal of Medical Genetics. 2002; 11:129–136.

Stevens MC, Fein DA, Dunn M, Allen D, Waterhouse LH, Feinstein C, et al. Subgroups of children with autism by cluster analysis: A longitudinal examination. Journal of the American Academy of Child and Adolescent Psychiatry. 2000; 39(3):346–352. [PubMed: 10714055]

Vermunt JK. Latent class modeling with covariates: Two improved three-step approaches. Political Analysis. 2010; 18:450–469.

Viding E, Blakemore SJ. Endophenotype approach to developmental psychopathology: implications for autism research. Behavioral Genetics. 2007; 37:51–60.

Waterhouse L, Gillberg C. Why autism must be taken apart. Journal of Autism and Developmental Disorders. 2014; 44:1788–1792. [PubMed: 24390538]

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 Developmental Disabilities. 2007; 22:33–38.

Wiggins LD, Levy SE, Daniels J, Schieve L, Croen LA, DiGuiseppi C, et al. Symptoms of autism spectrum disorder among children enrolled in the Study to Explore Early Development. Journal of Autism and Developmental Disorders. 2015a; 45:3183–3194. [PubMed: 26048040]

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. 2015b; 45:1271–1280. [PubMed: 25348175]

Wiggins LD, Robins DL, Adamson LB, Bakeman R, Henrich CC. Support for a dimensional view of autism spectrum disorders in toddlers. Journal of Autism and Developmental Disorders. 2012; 42:191–200. [PubMed: 21448751]

Wurpts IC, Geiser C. Is adding more indicators to a latent class analysis beneficial or detrimental? Results of a Monte–Carlo study. Frontiers in Psychology. 2014; 5:1–15. [PubMed: 24474945]

Table 1

Latent class variables for children with autism spectrum disorder enrolled in the Study to Explore Early Development (SEED)

SEED data source	Latent class variables	Scores used in latent class analysis	Scores indicating impairment
Autism diagnostic observation schedule	Autism symptom severity	Total severity scores from 1 to 10	Higher
Autism diagnostic interview-revised	Age at single word development	Item scores from 4 to 62 months	Higher
	Age at walking	Item scores from 7 to 43 months	
	History of regression	Item score dichotomized into yes (regression in either language or social domains reported) or no (regression in language or social domains not reported)	
	Insistence on sameness	Item scores representing compulsions/rituals, difficulties with minor changes in routines, and resistance to trivial changes in the environment dichotomized into yes (any reported) and no (not reported)	
	Repetitive behavior with objects	Item score dichotomized into yes (reported) and no (not reported)	
	Repetitive motor mannerisms	Item scores representing hand and finger mannerisms and other complex mannerisms dichotomized into yes (any reported) and no (not reported)	
	Restricted interests	Item scores representing unusual preoccupations, circumscribed interests, and unusual attachment to objects dichotomized into yes (any reported) and no (not reported)	
	Self-injurious behaviors	Item score dichotomized into yes (self-injurious behavior reported) and no (no self-injurious behavior reported)	
	Unusual sensory response	Item scores representing unusual sensory interests, undue sensitivity to noise, and negative response to specific sensory stimuli dichotomized into yes (any reported) and no (not reported)	
Birth certificate	Gestational age[a]	Gestational age scores from 23 to 43 weeks	Lower
Caregiver interview	Early recognition of epilepsy/seizure disorder	Item score dichotomized into yes (parent report of epilepsy/seizure disorder) or no (no parent report of epilepsy/seizure disorder)	Higher
Child behavior checklist	Aggressive behaviors, anxiety/depression, attention problems, emotional reactivity, somatic complaints, withdrawn behaviors	Domain t-scores from 50 to 100	Higher
Child sleep habits questionnaire	Sleep problems	Total problems scores from 0 to 91	Higher
Early Development Questionnaire	Problems with age at first social smile	Item scores dichotomized into yes (delayed social smile) and no (typical social smile)	Higher
Gastrointestinal Questionnaire	History of gastrointestinal symptoms[a]	Item score dichotomized into yes (history of gastrointestinal symptoms) or no (no history of gastrointestinal symptoms)	Higher
	Current diet restrictions	Item score dichotomized into yes (diet restrictions) or no (no diet restrictions)	
Mullen scales of early learning	Expressive language skills	Age equivalent scores from 2 to 70	Lower
	Fine motor skills	Age equivalent scores from 4 to 68	
	Receptive language skills	Age equivalent from 1 to 69	

SEED data source	Latent class variables	Scores used in latent class analysis	Scores indicating impairment
	Visual reception skills	Age equivalent scores from 5 to 69	
Social communication questionnaire	Social communication abilities	Total scores from 1 to 35	Higher

[a]These variables were ultimately dropped from the model because they did not distinguish latent classes

Table 2

Latent class fit statistics for children with autism spectrum disorder enrolled in the Study to Explore Early Development

Number of classes	Latent class distributions					Entropy	BIC[a]	SABIC[a]	LMR-LRT *p* values[a]
	1	2	3	4	5				
1	100	NA	NA	NA	NA	NA	80,528	80,401	NA
2	55	45	NA	NA	NA	0.93	78,305	78,096	<0.001
3	40	44	16	NA	NA	0.92	77,379	77,087	0.018
4	28	26	34	12	NA	0.92	76,722	76,347	0.001
5	21	25	25	19	10	0.91	76,493	76,036	0.567

[a] *BIC* Bayesian information criterion, *SABIC* sample adjusted BIC, *LMR-LRT* Lo-Mendell–Rubin likelihood ratio Test

J Autism Dev Disord. Author manuscript; available in PMC 2018 March 13.

Table 3

Item response probabilities and item response means (95% confidence interval) by latent class for children with autism spectrum disorder enrolled in the Study to Explore Early Development

	Latent class			
	1	**2**	**3**	**4**
Categorical variables (response probabilities)				
ADI-R history of regression	0.17 (0.11–0.23)$_A$	0.34 (0.27–0.42)$_B$	0.29 (0.22–0.36)$_{AB}$	0.25 (0.13–0.38)$_{AB}$
ADI-R insistence on sameness	0.72 (0.65–0.79)$_A$	0.63 (0.55–0.71)$_A$	0.66 (0.59–0.74)$_A$	0.90 (0.83–0.97)$_B$
ADI-R repetitive behavior with objects	0.77 (0.71–0.84)$_A$	0.94 (0.91–0.98)$_B$	0.82 (0.77–0.88)$_A$	0.96 (0.91–[#]1.00)$_B$
ADI-R repetitive motor mannerisms	0.74 (0.67–0.80)$_A$	0.96 (0.92–1.00)$_B$	0.78 (0.72–0.84)$_A$	0.83 (0.74–0.93)$_{AB}$
ADI-R restricted interests	0.86 (0.80–0.91)$_{AB}$	0.73 (0.66–0.80)$_A$	0.81 (0.75–0.87)$_{AB}$	0.92 (0.84–0.99)$_B$
ADI-R self-injurious behaviors	0.38 (0.31–0.46)$_A$	0.58 (0.50–0.66)$_B$	0.37 (0.30–0.44)$_A$	0.78 (0.68–0.89)$_C$
ADI-R unusual sensory response	0.91 (0.87–0.96)$_A$	0.97 (0.94–1.00)$_A$	0.94 (0.91–0.97)$_A$	0.97 (0.93–[#]1.00)$_A$
EDQ problems with age at first social smile	0.13 (0.08–0.18)$_A$	0.24 (0.16–0.31)$_{AB}$	0.15 (0.10–0.20)$_{AB}$	0.31 (0.19–0.42)$_B$
GI questionnaire current diet restrictions	0.26 (0.19–0.33)$_A$	0.36 (0.29–0.43)$_A$	0.30 (0.23–0.37)$_A$	0.40 (0.28–0.52)$_A$
Maternal interview early recognition of epilepsy/seizure disorder	0.00 (0.00–0.00)$_A$	0.13 (0.07–0.18)$_B$	0.02 ([#]0.00–0.04)$_A$	0.05 ([#]0.00–0.10)$_{AB}$
Continuous variables (response means)				
ADI-R age at single word development	19.89 (18.62–21.16)$_A$	30.58 (27.81–33.35)$_B$	25.16 (23.32–26.99)$_C$	24.32 (21.79–26.86)$_C$
ADI-R age at walking	13.69 (13.22–14.16)$_A$	16.31 (15.09–17.53)$_B$	14.11 (13.38–14.84)$_A$	13.60 (12.86–14.34)$_A$
ADOS autism severity	6.73 (6.51–6.95)$_A$	7.89 (7.64–8.13)$_B$	7.21 (6.98–7.44)$_C$	6.47 (6.11–6.82)$_A$
CBCL aggressive behaviors	55.94 (54.66–57.23)$_A$	61.94 (60.02–63.86)$_B$	57.98 (56.24–59.71)$_A$	76.18 (71.96–80.41)$_C$
CBCL anxiety/depression	53.60 (52.55–54.65)$_A$	56.24 (54.92–57.55)$_B$	53.38 (52.33–54.43)$_A$	69.56 (65.96–73.16)$_C$
CBCL attention problems	59.05 (57.73–60.37)$_A$	67.11 (65.60–68.61)$_B$	61.61 (60.20–63.03)$_A$	70.95 (68.94–72.97)$_C$
CBCL emotionally reactive	57.96 (56.49–59.44)$_A$	61.72 (59.89–63.55)$_B$	57.39 (55.75–59.02)$_A$	77.79 (74.13–81.45)$_C$
CBCL sleep problems	47.39 (45.88–48.91)$_A$	53.86 (51.95–55.78)$_B$	49.38 (47.65–51.11)$_A$	59.66 (56.02–63.29)$_C$
CBCL somatic complaints	57.20 (56.05–58.36)$_A$	60.79 (59.42–62.17)$_B$	58.16 (57.02–59.30)$_A$	67.72 (65.24–70.21)$_C$
CBCL withdrawn behaviors	64.92 (63.36–66.47)$_A$	76.38 (74.59–78.16)$_B$	66.98 (65.23–68.72)$_A$	76.66 (74.05–79.26)$_B$
MSEL expressive language skills	50.73 (48.69–52.76)$_A$	14.49 (12.77–16.21)$_B$	34.03 (31.98–36.08)$_C$	46.23 (42.47–49.99)$_A$
MSEL fine motor skills	54.49 (52.90–56.09)$_A$	23.07 (21.78–24.37)$_B$	37.56 (35.21–39.90)$_C$	49.98 (46.46–53.51)$_A$
MSEL receptive language skills	56.97 (54.92–59.01)$_A$	15.21 (13.40–17.02)$_B$	34.32 (32.04–36.60)$_C$	48.27 (43.91–52.62)$_D$
MSEL visual reception skills	61.33 (59.81–62.84)$_A$	23.13 (21.90–24.36)$_B$	40.50 (37.46–43.54)$_C$	53.66 (49.89–57.44)$_D$
SCQ social communication abilities	13.08 (12.08–14.08)$_A$	20.97 (20.10–21.83)$_B$	16.94 (15.95–17.94)$_C$	20.51 (19.14–21.88)$_B$

Subscripts indicate between-class differences based on confidence intervals that do not overlap (indicating statistically significant differences between latent classes);

[#]For interval estimates, a lower bound was reported as 0.00 when the lower bound estimate was <0.00 and an upper bound was reported as 1.00 when the upper bound estimate was >1.00

Table 4

Summary of between-class differences among latent classes of children with autism spectrum disorder enrolled in the Study to Explore Early Development

	Least impaired class			**Most impaired class**
Categorical variables				
ADI-R history of regression	1		2, 3, 4	
ADI-R insistence on sameness	1, 2, 3		4	
ADI-R repetitive behavior with objects	1, 3		2, 4	
ADI-R repetitive motor mannerisms	1, 3	4		2
ADI-R restricted interests	2	1, 3		4
ADI-R self-injurious behaviors	1, 3	2		4
ADI-R unusual sensory response		1, 2, 3, 4		
EDQ problems with age at first social smile	1, 2, 3		4	
GI questionnaire current diet restrictions		1, 2, 3, 4		
Maternal interview early recognition of epilepsy/seizure disorder	1, 3		2, 4	
Continuous variables				
ADI-R age at single word development	1	3, 4		2
ADI-R age at walking	1, 3, 4			2
ADOS Autism symptoms severity	1, 4		3	2
CBCL aggressive behaviors	1, 3		2	4
CBCL anxious/depressed	1, 3		2	4
CBCL attention problems	1, 3		2	4
CBCL emotionally reactive	1, 3		2	4
CBCL sleep problems	1, 3		2	4
CBCL somatic complaints	1, 3		2	4
CBCL withdrawn behaviors	1, 3		2, 4	
MSEL expressive language skills	1, 4		3	2
MSEL fine motor skills	1, 4		3	2
MSEL receptive language skills	1	4	3	2
MSEL visual reception skills	1	4	3	2

J Autism Dev Disord. Author manuscript; available in PMC 2018 March 13.

	Least impaired class ⇨		Most impaired class
SCQ social communication abilities	1	3	2, 4

J Autism Dev Disord. Author manuscript; available in PMC 2018 March 13.

Table 5

Sample characteristics by latent class for children with autism spectrum disorder enrolled in the Study to Explore Early Development (SEED)

Predicators	Total sample N(%)	Class 1: mild language delay with cognitive rigidity N(%)	Class 2: significant developmental delay with repetitive motor mannerisms N(%)	Class 3: general developmental delay N(%)	Class 4: mild language and motor delays with dysregulation N(%)
Child age					
Age	M = 59.35 months	M = 61.63 months	M = 59.07 months	M = 57.53 months	M = 59.58 months
Child ethnicity					
Hispanic	112 (15.84)	23 (11.44)	41 (21.81)	33 (14.04)	15 (18.07)
Non-Hispanic	595 (84.16)	178 (88.56)	147 (78.19)	202 (85.96)	68 (81.93)
Child race					
White	406 (57.43)	140 (69.65)	90 (47.87)	130 (55.32)	46 (55.42)
Black	134 (18.95)	22 (10.94)	53 (28.19)	42 (17.87)	17 (20.48)
Multiracial	86 (12.16)	21 (10.45)	16 (8.51)	35 (14.89)	14 (16.87)
Other	81 (11.46)	18 (8.96)	29 (15.43)	28 (11.92)	6 (7.23)
Child sex					
Female	127 (17.96)	31 (15.42)	39 (20.74)	44 (18.72)	13 (15.66)
Male	580 (82.04)	170 (84.58)	149 (79.26)	191 (81.28)	70 (84.34)
Maternal education					
High school or less	142 (20.46)	20 (10.10)	55 (29.89)	42 (18.26)	25 (30.49)
Some college	200 (28.82)	47 (23.74)	61 (33.15)	63 (27.39)	29 (35.37)
Bachelor’s degree	219 (31.56)	69 (34.85)	52 (28.26)	81 (35.22)	17 (20.73)
Master’s degree or higher	133 (19.16)	62 (31.31)	16 (8.70)	44 (19.13)	11 (13.41)
Primary language					
English	616 (88.51)	182 (91.46)	154 (83.70)	206 (89.18)	74 (90.24)
Non-English	80 (11.49)	17 (8.54)	30 (16.30)	25 (10.82)	8 (9.76)
Study site					
CA	112 (15.84)	32 (15.92)	28 (14.89)	42 (17.87)	10 (12.05)
CO	142 (20.08)	41 (20.40)	34 (18.09)	45 (19.15)	22 (26.51)
GA	138 (19.52)	39 (19.40)	51 (27.13)	38 (16.17)	10 (12.05)
MD	108 (15.28)	28 (13.93)	32 (17.02)	35 (14.89)	13 (15.66)
NC	104 (14.71)	31 (15.42)	24 (12.77)	38 (16.17)	11 (13.25)

Predicators	Total sample N(%)	Class 1: mild language delay with cognitive rigidity N(%)	Class 2: significant developmental delay with repetitive motor mannerisms N(%)	Class 3: general developmental delay N(%)	Class 4: mild language and motor delays with dysregulation N(%)
PA	103 (14.57)	30 (14.93)	19 (10.10)	37 (15.75)	17 (20.48)

Table 6

Adjusted odds ratios (AOR) with 95% confidence intervals (CI) evaluating the associations between covariates and latent class membership with Class 2 (significant developmental delay with repetitive motor behaviors) as the reference class

Predicators	Class 1: mild language delay with cognitive rigidity AOR (95% CI)	Class 3: general developmental delay AOR (95% CI)	Class 4: mild language and motor delays with dysregulation AOR (95% CI)
Child age			
Age	1.13 (1.08–1.19) ***	0.98 (0.95–1.02)	1.05 (1.00–1.11) *
Child ethnicity			
Hispanic	0.59 (0.29–1.21)	0.63 (0.33–1.19)	0.77 (0.34–1.73)
Non-Hispanic	Ref.	Ref.	Ref.
Child race			
White	Ref.	Ref.	Ref.
Black	0.27 (0.13–0.57) **	0.68 (0.37–1.25)	0.61 (0.28–1.33)
Multiracial	0.89 (0.39–2.00)	1.48 (0.72–3.02)	1.73 (0.71–4.24)
Other	0.47 (0.21–1.06)	0.68 (0.30–1.51)	0.44 (0.12–1.61)
Child sex			
Female	0.64 (0.34–1.21)	0.99 (0.56–1.74)	0.68 (0.32–1.44)
Male	Ref.		
Maternal education			
High school or less	Ref.	Ref.	Ref.
Some college	2.06 (0.98–4.32)	1.25 (0.68–2.29)	0.97 (0.47–1.99)
Bachelor's degree	2.96 (1.38–6.31) **	1.76 (0.95–3.27)	0.60 (0.26–1.41)
Master's degree or higher	10.44 (4.12–26.44) ***	3.13 (1.36–7.16) **	1.35 (0.48–3.85)
Primary language			
English	Ref.	Ref.	Ref.
Non-English	0.63 (0.30–1.33)	0.80 (0.37–1.74)	0.69 (0.22–2.17)
Study site			
CA	1.02 (0.41–2.53)	1.48 (0.62–3.54)	0.74 (0.23–2.35)
CO	1.30 (0.56–2.99)	0.98 (0.44–2.19)	1.40 (0.53–3.76)
GA	0.40 (0.17–0.93) *	0.57 (0.25–1.27)	0.34 (0.11–1.05)
MD	0.45 (0.18–1.13)	0.74 (0.34–1.64)	0.69 (0.24–1.96)
NC	Ref.	Ref.	Ref.
PA	1.12 (0.42–2.97)	1.45 (0.59–3.58)	1.89 (0.64–5.57)

Ref reference class (i.e., Class 2: significant developmental delay with repetitive motor behaviors)

* *p*-value < 0.05,

** *p*-value < 0.01,

*** *p*-value < 0.001