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Mapping the Relationship between Dysmorphology and Cognitive, Behavioral, and Developmental Outcomes in Children with Autism Spectrum Disorder

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Abstract

Previous studies investigating the association between dysmorphology and cognitive, behavioral, and developmental outcomes among individuals with autism spectrum disorder (ASD) have been limited by the binary classification of dysmorphology and lack of comparison groups. We assessed the association using a continuous measure of dysmorphology severity (DS) in preschool children aged 2–5 years (322 with ASD and intellectual disability [ID], 188 with ASD without ID, and 371 without ASD from the general population [POP]). In bivariate analyses, an inverse association between DS and expressive language, receptive language, fine motor, and visual reception skills was observed in children with ASD and ID. An inverse association of DS with fine motor and visual reception skills, but not expressive language and receptive language, was found in children with ASD without ID. No associations were observed in POP children. These results persisted after exclusion of children with known genetic syndromes or major morphologic anomalies. Quantile regression models showed that the inverse relationships remained significant after adjustment for sex, race/ethnicity, maternal education, family income, study site, and preterm

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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.

Conflict of Interest

The authors declare that they have no conflict of interest.

Ethical Approval

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Supporting Information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Appendix S1: Supporting information

birth. DS was not associated with autistic traits or autism symptom severity, behaviors, or regression among children with ASD with or without ID. Thus, DS was associated with a global impairment of cognitive functioning in children with ASD and ID, but only with fine motor and visual reception deficits in children with ASD without ID. A better understanding is needed for mechanisms that explain the association between DS and cognitive impairment in children with different disorders.

Lay Summary:

We examined whether having more dysmorphic features (DFs) was related to developmental problems among children with autism spectrum disorder (ASD) with or without intellectual disability (ID), and children without ASD from the general population (POP). Children with ASD and ID had more language, movement, and learning issues as the number of DFs increased. Children with ASD without ID had more movement and learning issues as the number of DFs increased. These relationships were not observed in the POP group. Implications are discussed.

Keywords

autism spectrum disorder; dysmorphic features; dysmorphology severity; intellectual disability; neurodevelopment

Introduction

Autism spectrum disorder (ASD) is a developmental disorder characterized by deficits in social communication and interaction and restricted and repetitive behaviors, interests, and activities [American Psychiatric Association, 2013]. Children with ASD manifest remarkable variability in the following areas: level of functioning; co-occurring behavioral, developmental, and medical conditions; and responses to medical and behavioral interventions [Miles & Hillman, 2000; Levy et al., 2010; Angkustsiri et al., 2011; Close, Lee, Kaufmann, & Zimmerman, 2012; APA, 2013; Wiggins et al., 2015a; Wiggins et al., 2017]. While the underlying causes of ASD are largely unknown, available evidence indicates that both genetic and environmental risk factors play an important role in ASD etiologies [Arndt, Stodgell, & Rodier, 2005; Miles, 2011; Kim & Leventhal, 2015; Ornoy, Weinstein-Fudim, & Ergaz, 2016; Schieve et al., 2018a; Bai et al., 2019]. Studies also suggest that the embryonic period is a critical exposure window affecting the risk of developing ASD [Arndt et al., 2005; Schieve et al., 2018b].

Dysmorphic features (DFs) are part of a broad spectrum of morphological characteristics. They are frequently interpreted as markers of atypical embryonic development. DFs are usually visible on physical examination, but in isolation, typically have no significant medical or surgical consequences. DFs are presumed to result from genetic and/or environmental disturbances that occur primarily during the first trimester of pregnancy [Smalley, Asarnow, & Spence, 1988; Miles et al., 2005]. DFs occur occasionally in members of the general population. However, studiesFV of DFs have reported them as more common among individuals with ASD, cancer, diabetes mellitus, learning disability, schizophrenia, and hyperactivity when compared to population controls [Waldrop & Goering, 1971;

Firestone & Peters, 1983; Mehes et al., 1986; Sivkov & Akabaliev, 2003; Weinberg, Jenkins, Marazita, & Maher, 2007; Merks et al., 2008; Ozgen, Hop, Hox, Beemer, & van Engeland, 2010; Angkustsiri et al., 2011; Seggers et al., 2014; Shapira et al., 2019].

A few studies have examined the association between DFs and cognitive, behavioral, and developmental outcomes among individuals with ASD by way of a comprehensive dysmorphology assessment. Miles and Hillman [2000] and Miles et al. [2005] conducted a systematic dysmorphology evaluation of 200 DFs and demonstrated that individuals with ASD with >6 DFs and/or microcephaly were more likely to have intellectual disability (ID), deficient verbal language skills, seizures, and brain MRI anomalies than those with <3 DFs and no microcephaly. Wong, Fung, and Wong [2014] replicated these results through a medical record review comparing patients with ASD with ≥1 DFs to those without DFs. Flor, Bellando, Lopez, and Shui [2017] used the autism dysmorphology measure approach [Miles et al., 2008], where an algorithm was used to define individuals with ASD as dysmorphic based on the presence of any DF in particular body areas, rather than on the total number of DFs. They extended previous findings by showing that ASD with DFs, compared to ASD without DFs, was associated with poorer adaptive behaviors and lower quality of life, but not associated with autism severity scores and problem behavioral scores. In contrast, Angkustsiri et al. [2011], using a modification of the Miles et al. [2005] classification approach, found that ASD with ≥3 DFs, compared to ASD with <3 DFs, was associated with seizures, but not intelligence test scores, receptive and expressive language skills, regression, or adaptive functioning skills.

All of the aforementioned association studies examined the association between DS and child outcomes by comparing two groups, ASD with one or more DFs versus ASD without or with fewer DFs, assuming homogeneity of risk within the groups and ignoring the continuous spectrum of the number of DFs in the population. Such a dichotomized approach precludes examination of an exposure–response relationship, which could provide evidence of possible causal relationships, and is not statistically optimal as it can result in both loss of power and inaccurate estimation [MacCallum, Zhang, Preacher, & Rucker, 2002; Altman & Royston, 2006]. Moreover, these studies used different cutoff scores to define categories of dysmorphology, which potentially led to inconsistent results and limited comparison across studies. Most studies only conducted bivariate analyses, and potential confounding effects were not taken into account. Previous studies were also limited in their ability to assess ASD subgroups, such as ASD with or without ID, and did not include a comparison group of children in the general population. Thus, it has not been possible to assess whether associations previously reported are specific to ASD subgroups or to all individuals.

The study to explore early development (SEED) is a multisite case–control study of genetic and environmental risk factors for ASD [Schendel et al., 2012; Wiggins et al., 2015b]. SEED has a large number of well-characterized young children with a range of developmental delays, including ASD and ID, which has allowed for ASD subgroup analyses and for control for potential confounding factors. Cases are classified based on in-depth standardized developmental assessments administered by research-reliable clinical study staff, rather than reports of past diagnoses. During the first phase of SEED data collection (SEED1), children who had some ASD characteristics noted on an ASD screen, and those

from the general population were administered thorough dysmorphology assessments. We examined the association between SEED1 dysmorphology classification [Shapira et al., 2019] and cognitive, behavioral, and developmental outcomes in children with ASD and ID, ASD without ID, and children without ASD from the general population, with a continuous classification of dysmorphology as the exposure, which allowed for assessing exposure–response relationships.

Method

Participants and Data Collection

Study participants were children enrolled in SEED1. Details of SEED1 can be found in Schendel et al. [2012]. Briefly, SEED1-eligible children were born between 2003 and 2006 and enrolled at 2–5 years of age. They resided in one of the six sites within California, Colorado, Georgia, Maryland, North Carolina, and Pennsylvania and lived with a knowledgeable caregiver (98% biological mothers) who could communicate in English or either English or Spanish in California and Colorado. Three groups of children were ascertained from each study site: children with ASD, children with other developmental delay or disorders (DD), and children from the general population (POP). Children considered for potential inclusion in the first two groups were ascertained from educational or health sources or family referral, and children considered as POP were ascertained from random samples of birth certificate records within each study site's catchment area. Information on family sociodemographic characteristics and child health history, including age, sex, race/ethnicity, maternal education, family income, birth defect or known genetic syndrome, other developmental conditions, and preterm birth, were collected from caregiver interview or birth certificate files.

Cognitive, behavioral, and developmental outcomes were obtained via administration of the Mullen scales of early learning (MSEL) [Mullen, 1995], autism diagnostic observation schedule (ADOS) [Lord, Rutter, DiLavore, & Risi, 1999; Lord et al., 2000; Gotham, Risi, Pickles, & Lord, 2007], and Autism Diagnostic Interview—Revised (ADI-R) [Lord, Rutter, & Le Couteur, 1994; Rutter et al., 2003b], as well as caregiver report on the child behavior checklist (CBCL) [Achenbach, 1992], and social responsiveness scale (SRS) [Constantino, 2002]. Four domains of age equivalent scores in the MSEL were used to determine early learning ability; a higher score indicates a less severe cognitive impairment. Expressive language scores measured the ability to use words and make sentences. Receptive language scores measured the ability to understand the verbal communication of another person. Fine motor scores measured small and precise movements that use the thumb and index finger. Visual reception scores measured the ability to understand and make sense of images. Internalizing and externalizing behavior *t*-scores in the CBCL were used to evaluate child behaviors. Internalizing behavior scores measured emotional reactions, symptoms of anxiety and depression, and social withdrawal. Externalizing behavior scores measured problems with attention and aggressive behavior. SRS total *t*-scores were used to assess autistic traits. SRS scores were obtained for five subscales: social awareness, social cognition, social communication, social motivation, and restricted interests and repetitive behavior. A higher CBCL or SRS score indicates more severe symptoms. History of language or social

regression was evaluated in the ADI-R. Autism symptom severity was measured by the ADOS calibrated severity scores and categorized as severe (8–10) or mild or moderate (4–7) autism symptoms.

Case Classification

Details on the SEED final classification algorithm were previously published [Wiggins et al., 2015b]. Caregivers of all enrolled children were asked to complete the social communication questionnaire (SCQ) [Rutter, Bailey, & Lord, 2003] to screen for possible ASD characteristics. Each family of an enrolled child with an SCQ score of ≥11, with a previous ASD diagnosis, or demonstrating ASD behaviors during the clinic visit, completed the ADOS and ADI-R for an ASD assessment. Children classified as ASD were those who met standard 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. Each child classified as DD was ascertained from educational or health sources or by family referral and did not have an SCQ score ≥11 or did not meet SEED ASD criteria. Each child classified as POP was ascertained from birth certificates and did not have an SCQ score ≥11 or did not meet SEED ASD criteria. The MSEL early learning composite score, which is a standard score based on scores of the aforementioned four domains, determined the presence (≤70) or absence (>70) of ID for children with ASD and children with non-ASD DD.

Dysmorphology Severity

Details of the dysmorphology examination and classification can be found in Shapira et al. [2019]. Study staff trained and overseen by clinical geneticists at each study site performed a systematic dysmorphology protocol, including an in-person examination, a series of photographs of each child with scans of both hands, sets of measurements from photographs and hand scans, and recording centiles for all measurements obtained. Clinical geneticists then reviewed a total of 397 potential DFs for each child within seven body regions—ears; eyes and eyebrows; growth and skin; head, hair, face, and neck; hands and feet; mouth, lips, and teeth; and nose and philtrum—with typically one geneticist responsible for each body region for all SEED1 participants. Each feature received a Likert score by a geneticist, indicating the degree to which the feature was dysmorphic: 0 = normal/absent, 1 = possible/questionable, 2 = mild, 3 = moderate, 4 = severe, or ND = no data. Two geneticists (S.K.S. and J.E.H.) also evaluated the responses to interview questions posed to each child's caregiver about previous diagnoses of birth defects and genetic syndromes and genetic testing in the child by a doctor or healthcare provider; the reported information was coded into three variables: nonchromosomal genetic syndromes, chromosomal anomalies, and major morphologic anomalies. When available, child medical records were reviewed to clarify diagnoses.

The approach to defining each physical feature as dysmorphic and developing the overall dysmorphology score for each child has been described in detail in Shapira et al. [2019].

Three racial/ethnic categories/ethnic categories were evaluated separately: non-Hispanic white (NHW), non-Hispanic black (NHB), and Hispanic. The POP group for each racial/ethnic category was utilized to determine the definition of "dysmorphic" for each feature.

The proportions of POP children and the Bayesian shortest 95% confidence intervals for Likert scores of ≥2, ≥3, and =4 were calculated for each feature, and the largest range of Likert scores that either included 5% or had an upper confidence limit ≤5% was selected as the Likert score range that defined the feature as dysmorphic. Features that had Likert scores of only 0 (normal/absent) or 1 (possible/questionable) for all children in both POP and ASD groups within a race/ethnicity category were not informative to the analysis and, thus, were excluded. Additionally, a small number of features (one among NHW and three among NHB children) were excluded as non-informative since the smallest frequency of Likert scores (i.e., =4) had a lower confidence limit that was >5%. After these exclusions, the total number of features available for analysis in children in the three racial/ethnic categories was 327.

Once each of the 327 features was assigned as either dysmorphic or non-dysmorphic in each child, a racial/ethnic-specific dysmorphology score was calculated for each child; the dysmorphology score was defined as the total number of DFs that a child had, divided by the total number of features for which the child had received any Likert score, and then multiplied by 100. The expected values of the log-normal distribution of dysmorphology scores were utilized to convert the dysmorphology score of each child in the POP group to a corresponding percentile of the log-normal distribution. The racial/ethnic-specific log-normal distributions of dysmorphology scores of children in the POP group were similarly used to convert the dysmorphology scores of the corresponding racial/ethnic groups of children with ASD or DD to percentiles. These converted dysmorphology scores represented the severity of dysmorphology; a higher value implied higher dysmorphology severity (DS).

Statistical Analysis

This analysis is limited to SEED1 children who received a classification of ASD with ID, ASD without ID, or POP and who underwent a dysmorphology review. Due to resource constraints, dysmorphology review was prioritized for ASD cases and POP controls and, thus, was completed for only a subset of children in the DD group, in which those with ID henceforth referred to as “non-ASD ID” in this report—were included in a supplementary analysis. Medians of DS, MSEL, CBCL, and SRS scores by study group were calculated, and the medians were compared using Mood’s median test. The distributions of sex, race/ethnicity, maternal education, family income, study site, preterm birth, and the major morphologic anomaly or known genetic syndrome (includes both nonchromosomal genetic syndromes and chromosomal anomalies) by study group were examined and compared using chi-square tests. The association between DS and MSEL domain scores, CBCL domain scores, and SRS total scores were examined using Spearman correlation [Akoglu, 2018].

Logistic regression was used to model the association with DS for binary outcome variables, and quantile regression (QR) was used for continuous outcome variables [Koenker & Bassett, 1978; Koenker, 2005; Cook & Manning, 2013]. QR models the relation between a set of independent variables and specific centiles (or quantiles) of the response variable. A QR parameter estimates the change in a specified quantile of the response variable produced by one unit of change in the independent variable when all other independent variables are

held constant. In multivariate analyses, child sex, race/ethnicity, maternal education, family income, study site, and preterm birth were adjusted in the models. We did not include child age in the models since the age range of our participants was narrow and ASD and POP groups had the same median age (4 years) and age range (2–5 years) at the time of enrollment. A subgroup data analysis was conducted after excluding 76, 41, and 44 children with known genetic syndromes or major morphologic anomalies from children with ASD with ID, children ASD without ID, and POP children, respectively, although only bivariate Spearman correlation analyses were conducted due to relatively small sample sizes. All analyses were conducted using SAS 9.4 (SAS Institute Inc., Cary, NC). All statistical tests were two-sided, and *P*-values <0.05 were considered statistically significant.

Spearman correlation was also used to examine the relationship between DS and cognitive functioning, behaviors, and autism traits in the supplementary analysis of 68 children with non-ASD ID.

Results

Characteristics of the Study Population

A total of 322 children with ASD and ID, 188 with ASD without ID, and 371 children in the POP group met the selection criteria and were included in the primary analysis.

Table 1 displays demographic and other characteristics by study group. When compared to POP children, children with ASD with or without ID were more likely to be male and to have been born with a major morphologic anomaly or have a known genetic syndrome; children with ASD without ID were more likely to be NHW; children with ASD and ID were less likely to have been born to mothers with college or higher education and in high-income families (≥$90K).

When compared to children with ASD and ID, children with ASD without ID were more likely to be NHW, to have been born to mothers with college or higher education and in high-income families (≥$90K). The distributions of study site across study groups were different.

Table 2 displays medians of continuous outcomes and DS scores by the study group. Overall, children with ASD with or without ID had significantly lower median scores for expressive language, receptive language, and fine motor skills, and significantly higher median scores for internalizing behavior, externalizing behavior, SRS, and DS compared to POP children. The median of visual reception scores for children with ASD and ID was significantly lower than the median score in the POP group, but the median for children with ASD without ID was identical to the median score in the POP group. When compared to ASD without ID, children with ASD and ID had significantly lower median scores for expressive language, receptive language, fine motor, and visual reception skills and higher median scores for SRS autism traits, ADOS autism symptom severity, and DS. Median scores for internalizing and externalizing behaviors were almost identical between the ASD and ID and the ASD without ID groups.

Outcomes in Relation to DS

The results of Spearman correlation analysis in Table 3 indicated that DS was inversely associated with expressive language, receptive language, fine motor skills, and visual reception skills among children with ASD and ID. An inverse association between DS and fine motor skills and visual reception skills, but not expressive language and receptive language, was observed in children with ASD without ID. Among children in the POP group, DS was not significantly associated with the four MSEL domains. DS was not significantly associated with internalizing or externalizing behaviors, or autism traits or autism symptom severity in any of the groups examined. After excluding 76 and 41 children with major morphologic anomalies or known genetic syndromes from ASD with ID and ASD without ID groups, respectively, the inverse associations observed were still statistically significant, although associations between DS and fine motor skills and visual reception skills among children with ASD and ID were attenuated (Table 3).

Multivariate QR analysis results in Table 4 showed that after adjustment for child sex, race/ethnicity, maternal education, family income, study site, and preterm birth, the inverse associations at the median level of the outcomes remained statistically significant in children with ASD and ID for expressive language, receptive language, fine motor skills, and visual reception skills; and in children with ASD without ID for fine motor skills and visual reception skills. DS was not associated with autistic traits, internalizing and externalizing behaviors, or symptom severity, or with developmental regression among ASD with or without ID or POP children (Tables 4 and 5). After excluding children with major morphologic anomalies or known genetic syndromes from ASD with or without ID groups, sample sizes were inadequate for QR analyses.

The supplementary analysis of 68 children with non-ASD ID also showed an inverse association between DS and expressive language, receptive language, fine motor skills, and visual reception skills. We did not find a significant association between DS and behaviors or autistic traits in children with non-ASD ID (Table S1). Parent-reported conditions among children with non-ASD ID are presented in Table S2.

Discussion

Our study demonstrated that DS was inversely associated with measures of early learning ability in each of the four MSEL domains—expressive language, receptive language, fine motor skills, and visual reception skills—in children with ASD and ID. DS was inversely associated with only fine motor skills and visual reception skills, but not expressive language or receptive language in children with ASD without ID. These associations among children with ASD with and without ID were consistent with an exposure–response relationship that remained significant after controlling for sex, race/ethnicity, maternal education, family income, study site, and preterm birth. These associations were also observed after excluding children with ASD with major morphologic anomalies or known genetic syndromes. There were no observed associations between DS and outcomes in the POP group. A supplementary analysis of 68 children in the non-ASD ID group showed an inverse association between DS and expressive language, receptive language, fine motor skills, and visual reception skills. The association with expressive language among non-ASD ID

children was not statistically significant ($P = 0.06$); this may be due to the small sample size, and the magnitude of the association (Spearman correlation coefficient of −0.22) matched that of the association among children with ASD and ID. However, these analysis results of 68 children need to be confirmed in future studies that include a large sample of non-ASD ID children. In addition, there was not a significant association between DS and autistic traits or symptom severity, a finding that replicates those of Flor et al. [2017]. Taken together, these findings suggest that DFs are likely only related to a global cognitive functioning of neurodevelopment for children with ID, regardless of ASD status, and ID status modifies the associations with expressive and receptive language impairments in children with ASD.

The finding of an inverse association between DS and cognitive functioning is in line with previous studies [Miles et al., 2005; Wong et al., 2014; Flor et al., 2017], although the methods of assessing dysmorphology were different. Miles et al. [2005] found that individuals with ASD with >6 DFs and/or microcephaly had lower intelligence quotient (IQ)/developmental quotient scores (mean = 53.1) than those with <3 DFs and no microcephaly (mean = 70.4, $P = 0.0009$). Wong et al. [2014] found that individuals with ASD with DFs were more likely to have mild or moderate learning disabilities than individuals without DFs ($P < 0.01$). Flor et al. [2017] found that “dysmorphic” individuals with ASD had lower IQ scores (mean = 67.7) than “non-dysmorphic” individuals with ASD (mean = 77.5, $P = 0.025$). Multiple replications of these findings suggest that the prenatal development of DFs may be markers of differences in the development of cognitive processes that manifest as developmental disabilities after birth. Our subgroup analyses of children with ASD by ID extended the finding by suggesting that ID status modifies the association with expressive and receptive language impairments in children with ASD, supporting the suggestion that ASD with ID may be causally distinct from ASD without ID [Li et al., 2016].

We found no associations between DS and internalizing or externalizing behaviors among ASD with or without ID or POP groups. The finding of no associations with behaviors is consistent with the finding of Flor et al. [2017]. In addition, we did not find DS to be associated with a history of regression, which is consistent with the finding of Angkustsiri et al. [2011]. Children with ASD with ID had a higher median DS score than children with ASD without ID or children in the POP group (ASD with ID, median = 82; ASD without ID, median = 70; POP, median = 50). In general, a high DS score represents the presence of multiple DFs, which is often marker of developmental aberrations caused by genetic conditions or gestational exposures affecting prenatal development. An overabundance of DFs may indicate potential etiologies and predict outcomes. Children with ASD with ID had the highest DS, thus they could have had the most severe developmental aberrations that might explain the association of DS with a global impairment in cognitive functioning. Children with ASD without ID could have had less severe developmental aberrations, yielding only fine motor and visual reception deficits. Since POP children, overall, had much lower DS scores, it is not surprising that we did not observe associations between DS and cognitive functioning in the POP group. DFs in the POP group could possibly represent the normal variability of typical development as the POP group served as the basis for defining each feature as dysmorphic or not [Shapira et al., 2019].

The causal mechanisms of DFs may be explained by pleiotropic effects during early organogenesis [Ploeger, Raijmakers, van der Maas, & Galis, 2010]. The early development of many body parts, including the brain and skin, which both develop from ectoderm, are susceptible to disturbances. A disturbance in brain development during early organogenesis could affect other body parts, and vice versa. Although genetic syndromes and major morphologic anomalies are typically associated with DFs, interestingly, the inverse associations we found remained significant among children with ASD with or without ID after excluding those known to have genetic syndromes and major morphologic anomalies. These inverse associations could be interpreted as children with ASD with DFs being causally distinct from children with ASD without DFs. Thus, further characterizing subgroups of children with ASD with or without DFs could lead to the identification of risk factors for atypical development and inform clinical management. In terms of the latter, it may be prudent for healthcare providers and developmental intervention specialists who work with children with ASD and their families to screen for nonverbal delays when there is an overabundance of DFs without co-occurring ID. This type of screening approach may lead to earlier detection of developmental problems that impact health outcomes and encourage optimized treatment of children with ASD based on phenotypic presentation [Beversdorf et al., 2016].

Our study has a number of strengths. First, the DS exposure variable was rigorously derived based on 327 physical features and a population control group that served as the basis for defining each feature as dysmorphic or not. In other words, we have taken a further step to define what dysmorphic represents in light of normal population variation. Second, the analytic approach allowed us to assess the exposure–response association of DS on outcomes and to avoid potential measurement errors that might have been caused by using arbitrary cutoffs to dichotomously classify children based on a discrete number of DFs. Third, we also evaluated the associations in the POP group and a non-ASD ID group in addition to each ASD subgroup in order to understand whether the associations are specific to children with ASD with or without ID, or to all individuals. To our knowledge, no previous study has examined these associations among individuals with ASD with or without ID and among general population controls in the same study population. Lastly, our study participants have a smaller age range compared to many previous studies. The narrow age range can minimize the variation that might occur as physical features and the extent of DFs change with the growth of the child (examples described in Allanson, 1989; Cole & Hughes, 1994; Braddock, Henley, & Maria, 2007; Cung et al., 2015).

Our study also has a number of limitations. First, the results of the study should not be generalized to older children and adults as participants in this analysis were preschool-age (median = 4 years old), and milder forms of ASD might not be recognized until later in childhood or even into adolescence and adulthood. Second, some health conditions and behavior or social outcomes were collected from parent-reports via a caregiver interview rather than by direct assessment of the child. These reported data might be subject to recall bias. Third, the non-ASD-ID group is small, so our findings from this group cannot readily be generalized to larger populations of children with other DDs who have ID. Lastly, selection bias should be considered as dysmorphology reviews were performed only on those children who had completed dysmorphology assessment and who had achieved study

completion [Bradley et al., 2018]. Bradley et al. assessed whether participant demographic and administrative factors predicted study completion and found that differences in completion by mother's race and education were notable. We adjusted all multivariate analyses in the current study for race/ethnicity, maternal education, sex, family income, and preterm birth. There may be other important study completion-associated factors that we are not aware of. However, we have no reason to believe that a child's DS would have affected study completion.

In summary, this is the first study to examine the associations between a continuous measure of DS and cognitive, behavioral, and developmental outcomes within ASD phenotypic subgroups and a comparison group of race/ethnicity-specific general population controls. Our study demonstrated that DS was inversely associated with expressive language, receptive language, fine motor skills, and visual reception skills in children with ASD and ID. DS was inversely associated only with fine motor skills and visual reception skills, but not the expressive or receptive language in children with ASD without ID. These associations suggest that the presence of numerous DFs may only be linked to cognitive impairments of children with ASD and ID, and ID status modifies the associations with expressive and receptive language impairments in children with ASD. No associations were observed in POP children. Further characterization of subgroups of children with ASD with or without ID and with or without DFs might be conducive to the identification of risk factors for atypical development, which could inform clinical management.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table 1.

Characteristics of Study Participants by Case Status

	ASD with ID *n* = 322 (%)	ASD without ID *n* = 188 (%)	POP *n* = 371 (%)	*P*-value† (ASD with ID vs. POP)	*P*-value† (ASD without ID vs. POP)	*P*-value† (ASD with ID vs. ASD without ID)
Sex						
Male	255 (79.2)	159 (84.6)	198 (53.4)	<0.001	<0.001	0.134
Female	67 (20.8)	29 (15.4)	173 (46.6)			
Race/ethnicity						
Non-Hispanic white	161 (50.0)	147 (78.2)	185 (49.9)	0.450	<0.001	<0.001
Non-Hispanic black	94 (29.2)	22 (11.7)	96 (25.9)			
Hispanic	67 (20.8)	19 (10.1)	90 (24.3)			
Maternal education						
High school or less	88 (27.3)	27 (14.4)	66 (17.8)	0.004	0.472	0.001
Some college	94 (29.2)	50 (26.6)	104 (28.0)			
College degree or higher	140 (43.5)	111 (59.0)	201 (54.2)			
Family income						
<$50K	138 (45.3)	43 (23.1)	114 (32.1)	<0.001	0.003	<0.001
$50K-$89K	84 (27.5)	62 (33.3)	73 (20.6)			
≥$90K	83 (27.2)	81 (43.5)	168 (47.3)			
Study site						
California	41 (12.7)	21 (11.2)	70 (18.9)	0.022	0.002	0.054
Colorado	58 (18.0)	48 (25.5)	56 (15.1)			
Georgia	73 (22.7)	31 (16.5)	98 (26.4)			
Maryland	64 (19.9)	25 (13.3)	44 (11.9)			
North Carolina	45 (14.0)	36 (19.2)	56 (15.1)			
Pennsylvania	41 (12.7)	27 (14.4)	47 (12.7)			
Major morphologic anomaly or known genetic syndrome						
Yes	76 (23.8)	41 (21.8)	44 (11.9)	<0.001	0.002	0.616
No	244 (76.3)	147 (78.2)	327 (88.1)			
Preterm birth						
Yes (<37 weeks)	54 (16.8)	33 (17.7)	46 (12.5)	0.105	0.098	0.812
No (≥37 weeks)	267 (83.2)	154 (82.4)	323 (87.5)			

Abbreviations: ASD, autism spectrum disorder group; ID, intellectual disability; *n*, the total number of subjects sampled; POP, general population group.

† *p*-value derived from a chi-square test.

Table 2.

Medians of Cognitive Functioning, Internalizing and Externalizing Behaviors, Autism Traits and Severity, and Dysmorphology Severity Scores by Case Status

	ASD with ID median (95% CI)	ASD without ID median (95% CI)	POP median (95% CI)	*P*-value† (ASD with ID vs. POP)	*P*-value† (ASD without ID vs. POP)	*P*-value† (ASD with ID vs. ASD without ID)
Cognitive functioning (MSEL)						
Expressive language (age equivalent)	29 (27, 32)	48 (46, 51)	60 (58, 60)	<0.001	<0.001	<0.001
Receptive language (age equivalent)	29 (28, 31)	57 (55, 59)	62 (59, 62)	<0.001	<0.001	<0.001
Fine motor skills (age equivalent)	31 (30, 34)	53 (51, 55)	59 (59, 62)	<0.001	<0.001	<0.001
Visual reception skills (age equivalent)	31 (30, 34)	60 (60, 66)	60 (57, 60)	<0.001	0.334	<0.001
Behaviors (CBCL)						
Internalizing behaviors (*t*-score)	63 (62, 64)	62 (60, 64)	45 (43, 45)	<0.001	<0.001	0.562
Externalizing behaviors (*t*-score)	60 (59, 61)	59 (57, 61)	43 (42, 44)	<0.001	<0.001	0.176
Autism traits (SRS)						
SRS (total *t*-score)	75 (73, 77)	71 (69, 74)	47 (46, 47)	<0.001	<0.001	0.019
Autism symptom severity (ADOS)						
ADOS calibrated severity score	7 (7–8)	6 (6–7)	NA	NA	NA	<0.001
Dysmorphology assessment						
Dysmorphology severity	82 (79, 86)	70 (59, 75)	50 (45, 55)	<0.001	<0.001	<0.001

Abbreviations: ADOS, autism diagnostic observation schedule; ASD, autism spectrum disorder group; CBCL, child behavior checklist; CI, confidence interval; ID, intellectual disability; MSEL, Mullen scales of early learning; POP, general population group; SRS, social responsiveness scale.

† *P*-value derived from a Mood's median test to test the hypothesis that the medians are the same for the two groups.

Table 3.

Bivariate Analysis of the Relationship Between Dysmorphology Severity and Cognitive Functioning, Internalizing and Externalizing Behaviors, and Autism Traits and Severity by Case Status

Outcome	ASD with ID *n* = 322 Spearman correlation coefficient (95% CI)	ASD without ID *n* = 188 Spearman correlation coefficient (95% CI)	POP *n* = 371 Spearman correlation coefficient (95% CI)
Including children with major morphological anomalies or known genetic syndromes			
Cognitive functioning (MSEL)			
Expressive language (age equivalent)	−0.22 (−0.32, −0.12) ***	−0.12 (−0.26, 0.03)	0.04 (−0.07, 0.14)
Receptive language (age equivalent)	−0.21 (−0.31, −0.10) ***	−0.12 (−0.26, 0.02)	0.04 (−0.06, 0.14)
Fine motor skills (age equivalent)	−0.30 (−0.39, −0.19) ***	−0.23 (−0.36, −0.09) **	0.00 (−0.10, 0.11)
Visual reception skills (age equivalent)	−0.24 (−0.34, −0.13) ***	−0.22 (−0.35, −0.08) **	−0.01 (−0.11, 0.10)
Behaviors (CBCL)			
Internalizing behaviors (*t*-score)	−0.02 (−0.13, 0.09)	−0.10 (−0.24, 0.04)	−0.07 (−0.18, 0.03)
Externalizing behaviors (*t*-score)	0.02 (−0.10, 0.13)	−0.11 (−0.25, 0.04)	−0.02 (−0.13, 0.08)
Autism traits (SRS)			
SRS (total t-score)	0.02 (−0.09, 0.13)	−0.03 (−0.17, 0.11)	0.05 (−0.05, 0.15)
Autism symptom severity (ADOS)			
ADOS calibrated severity score	0.03 (−0.08, 0.14)	0.05 (−0.09, 0.19)	NA
Children without major morphologic anomalies or known genetic syndromes			
	ASD with ID ***n* = 244**	**ASD without ID** ***n* = 147**	**POP** ***n* = 327**
Cognitive functioning (MSEL)			
Expressive language (age equivalent)	−0.18 (−0.30, −0.06) **	−0.16 (−0.31, 0.01)	0.05 (−0.06, 0.16)
Receptive language (age equivalent)	−0.19 (−0.31, −0.06) **	−0.13 (−0.29, 0.03)	0.06 (−0.05, 0.17)
Fine motor skills (age equivalent)	−0.19 (−0.31, −0.07) **	−0.26 (−0.40, −0.10) **	0.03 (−0.08, 0.14)
Visual reception skills (age equivalent)	−0.14 (−0.26, −0.02) *	−0.27 (−0.41, −0.11) **	0.00 (−0.11, 0.11)

Abbreviations: ADOS, autism diagnostic observation schedule; ASD, autism spectrum disorder group; CBCL, child behavior checklist; CI, confidence interval; ID, intellectual disability; MSEL, Mullen scales of early learning; *n*, the total number of subjects sampled; POP, general population group; SRS, social responsiveness scale.

* 0.01 ≤ *P*-value <0.05.

** 0.001 ≤ *P*-value <0.01.

***P-value <0.001, derived to test the hypothesis that the correlation coefficient is 0.

Table 4.

Quantile Regression Analysis of the Relationship Between Dysmorphology Severity and Cognitive Functioning, Internalizing and Externalizing Behaviors, and Autism Traits and Severity by Case Status

	ASD with ID *n* = 322		ASD without ID *n* = 188		POP *n* = 371	
Outcome	**Unadjusted coefficient[a] (95% CI)**	**Adjusted[b] coefficient[a] (95% CI)**	**Unadjusted coefficient[a] (95% CI)**	**Adjusted[b] coefficient[a] (95% CI)**	**Unadjusted coefficient[a] (95% CI)**	**Adjusted[b] coefficient[a] (95% CI)**
Cognitive functioning (MSEL)						
Expressive language (age equivalent)	−0.15 *** (−0.23, −0.07)	−0.17[c] *** (−0.25, −0.09)	−0.07 (−0.15, 0.01)	−0.04 (−0.11, 0.04)	0.00 (−0.05, 0.05)	0.00 (−0.04, 0.04)
Receptive language (age equivalent)	−0.08 * (−0.15, −0.01)	−0.10 * (−0.17, −0.02)	−0.09 * (−0.16, −0.02)	0.00 (−0.07, 0.07)	0.00 (−0.06, 0.06)	0.01 (−0.02, 0.04)
Fine motor skills (age equivalent)	−0.16 *** (−0.22, −0.11)	−0.15 *** (−0.21, −0.09)	−0.10 ** (−0.16, −0.03)	−0.08 * (−0.16, −0.01)	0.00 (−0.05, 0.05)	0.00 (−0.03, 0.03)
Visual reception skill (age equivalent)	−0.15 *** (−0.23, −0.07)	−0.13 *** (−0.19, −0.07)	−0.12 *** (−0.19, −0.05)	−0.07 * (−0.12, −0.01)	0.00 (−0.04, 0.04)	0.00 (−0.03, 0.03)
Behaviors (CBCL)						
Internalizing behaviors (t-score)	0.00 (−0.04, 0.04)	0.00 (−0.04, 0.04)	0.00 (−0.07, 0.07)	−0.01 (−0.08, 0.05)	−0.03 (−0.07, 0.02)	−0.04 (−0.09, 0.01)
Externalizing behaviors (*t*-score)	0.00 (−0.05, 0.05)	0.02 (−0.03, 0.08)	−0.05 (−0.14, 0.05)	−0.02 (−0.12, 0.07)	−0.02 (−0.06, 0.03)	−0.01 (−0.05, 0.04)
Autism traits (SRS)						
SRS (total t-score)	0.03 (−0.04, 0.09)	0.02 (−0.04, 0.07)	−0.02 (−0.13, 0.10)	−0.03 (−0.13, 0.08)	0.00 (−0.03, 0.03)	0.01 (−0.02, 0.04)
Autism symptom severity (ADOS)						
ADOS calibrated severity score	0.00 (−0.01, 0.01)	−0.00 (−0.01, 0.01)	0.00 (−0.01, 0.01)	0.07 (−0.00, 0.02)	NA	NA

Note: ADOS, autism diagnostic observation schedule; ASD, autism spectrum disorder group; CBCL, child behavior checklist; CI, confidence interval; ID, intellectual disability; MSEL, Mullen scales of early learning; *n*, the total number of subjects sampled; POP, general population group; SRS, social responsiveness scale.

* 0.01 ≤ *P*-value <0.05.

** 0.001 ≤ *P*-value <0.01.

*** *P*-value <0.001, derived to test the hypothesis that the coefficient is 0.

[a] Coefficients of dysmorphology severity, derived from quantile regression models for the quantile level of outcome variables (0.5).

[b] Adjustment factors included in the models are sex, race/ethnicity, maternal education, family income, study site, and preterm birth.

[c]The estimated coefficient of −0.17 can be interpreted as the median of expressive language age equivalent decreased by about 0.17 for every one-unit increase in DS score while holding all the adjustment factors constant (all other coefficients in the table are similarly interpreted).

Table 5.

Logistic Regression Analysis of the Relationship Between Dysmorphology Severity and History of Regression Among Children With ASD

	ASD with ID			ASD without ID		
Outcome	***n* (%)**	**Unadjusted odds ratio (95% CI)**	**Adjusted[a] odds ratio (95% CI)**	***n* (%)**	**Unadjusted odds ratio (95% CI)**	**Adjusted[a] odds ratio (95% CI)**
ADI-R						
History of regression						
Yes	93 (30.0)			29 (16.5)		
No	217 (70.0)	0.99 (0.98, 1.00)	0.99 (0.98, 1.00)	147 (83.5)	1.00 (0.99,1.02)	1.00 (0.98, 1.02)

Abbreviations: ADI-R, autism diagnostic interview—revised; ASD, autism spectrum disorder group; CI, confidence interval; ID, intellectual disability; *n*, the total number of subjects sampled.

[a]Adjustment factors included in the logistic regression models are sex, race/ethnicity, maternal education, family income, study site, and preterm birth.