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Diagnosis of Autism Spectrum Disorder After Age 5 in Children Evaluated Longitudinally Since Infancy

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Abstract

Objective: The diagnosis of autism spectrum disorder (ASD) has been found to be remarkably stable but few studies have followed children not initially diagnosed with ASD beyond age 3 to examine late or delayed diagnoses. The current study used a prospective familial-risk design to identify children who had undergone multiple comprehensive assessments in preschool and were determined to be ASD-negative, only to meet criteria for ASD when tested in middle childhood.

Method: Data were pooled across three research teams studying later-born siblings of children with ASD. Fourteen children met inclusion criteria for the Late Diagnosed group and were compared to a large sample of high- and low-risk siblings from the same sites who had ASD or typical development (TD) outcomes at age 3.

Results: As a group, the Late Diagnosed children scored between the TD and ASD groups on most measures administered at age 3 and differed significantly from the ASD group on most measures. However, there was significant heterogeneity among the Late Diagnosed cases. Seven showed very little evidence of ASD in preschool, while seven demonstrated subtle, subthreshold symptomatology.

Conclusion: Some children with ASD may present with a subtle phenotype early in life or show a prolonged time course of symptom development. This emphasizes the need for screening and surveillance schedules that extend past 36 months and continued evaluation of any child who presents with atypical early development and/or high-risk status. The findings also shed light on reasons why the mean age of ASD diagnosis remains over 4 years.

Keywords

autism spectrum disorder; diagnosis; diagnostic stability

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Introduction

The mean age of autism spectrum disorder (ASD) diagnosis in the United States is currently 4.3 years and has not changed appreciably over the past decades.[1] This indicates that diagnosis after the preschool years is not uncommon. In large part this is due to delay in referrals for diagnostic evaluation. Much research has been done to identify factors related to age of diagnosis, finding that minority race/ethnicity, lower socioeconomic status and parental education levels, residence outside a metropolitan area, and diagnostic overshadowing are all significant contributors to delayed referral.[2] Of great interest are children who have in fact had early developmental evaluations performed, but still experience a delay in recognition of ASD.

Many studies have examined the stability of an ASD diagnosis,[3] but children not initially diagnosed have rarely been followed; that is, 'stability' is generally equated with the positive predictive value of an initial diagnosis. Few studies have reassessed children not initially regarded as having ASD to provide insight into the phenomenon of late or missed diagnoses. One study[4] examined 692 consecutive referrals to a neurodevelopmental evaluation center, identified all children (n=18) with a preschool diagnosis of severe receptive language delay, and reassessed them at a mean age of 8 years. All 18 met criteria for ASD at the later evaluation. Another study reported on 23 children, initially evaluated as preschoolers at an autism diagnostic clinic, who were reassessed at a mean age of 11 years.[5] Of the nine children who had not received an ASD diagnosis in preschool, four did so in school age. In both studies, the children subsequently diagnosed with ASD had been identified with early delays in language or cognitive function, which may have overshadowed social impairments or made them appear secondary.

The largest investigation was done by Davidovitch and colleagues,[6] who reviewed medical records, linked to a population-based registry, of 221 children diagnosed with ASD after age 6 who had been seen for developmental evaluation before age 6 and been found to be ASD-negative. Their initial preschool diagnoses included language, motor, and cognitive delays. Fewer than half of the children had features suggestive of ASD in their preschool medical records. The authors offered four potential explanations for the delayed identification of ASD: 1) diagnostic overshadowing by other conditions in the initial assessment, 2) increasing symptoms over time, 3) missed symptoms in the preschool evaluations, and 4) inaccurate diagnosis after age 6.

Prospective studies of high-risk infants offer a research strategy that could be informative to understanding why some children are diagnosed years after an initial ASD-negative evaluation. In such studies, infants at risk for ASD due to family history are enrolled in the first year of life and assessed for ASD multiple times in infancy and preschool, regardless of the presence or severity of symptoms. No clinical referral is required which, particularly for children with less severe impairments, often would not occur until school entry.[2] Brian et al.[7] followed such a high-risk cohort (n=67) to middle childhood (mean age 9 years) and found six children who were considered non-ASD at age 3 but later met diagnostic criteria for ASD. Shephard and colleagues[8] similarly identified five children, from a sample of 42 high-risk siblings, who had not received an ASD diagnosis at age 3 but were diagnosed at age 7.

The current study combines the later-diagnosed cases from the two previously published samples[7,8] with those from a third site studying high-risk infant siblings to differentiate among potential explanations for delayed diagnosis.[6] In addition to the power afforded by a larger sample, a strength of this paper is the prospective study design, which 1) provides natural controls for factors that can limit access to diagnostic assessments[2] and 2) follows children whether clinical concerns were present or not. The population-based mean age of diagnosis of 4.3 years[1] is driven largely by children who did not receive an early referral, not by children who were referred early and not diagnosed.[6] Thus, focusing on a sample that was assessed for ASD at multiple time points, without an initial clinical referral, may be particularly informative to the pressing question of why some children are not diagnosed until middle childhood.

Method

Participants

The present analyses were carried out using data from three research teams whose procedures, measures, and assessment schedules were similar enough to permit data pooling. Informed consent was obtained at each site prior to data collection, as well as Institutional Review Board approval to pool and analyze de-identified data across sites.

Participants were later-born biological siblings of children with ASD (high-risk group) or typical development (low-risk group). Inclusion in the high-risk group required an ASD diagnosis, documented by a clinical report and/or an appropriate screening measure (e.g., Social Communication Questionnaire), in the affected older sibling and no identified neurological or genetic condition that could account for an ASD diagnosis (e.g., fragile X syndrome). Inclusion criteria for the low-risk group were no family history of ASD in first or second degree relatives and at least one older sibling with typical development, verified by intake questionnaire or standardized instrument (e.g., Social Communication Questionnaire). Additional inclusion criteria for both groups were birth after 35 weeks gestation, maximum enrollment age of 18 months, initial outcome assessment at 3 years, and availability of later diagnostic assessments between ages 5 and 9. The present paper focuses on all children (n=14) from the participating groups who did not receive a diagnosis at 3 years but met ASD criteria at a follow-up school-age visit. Comparison is made to the remaining children comprising the samples at each site (470 high-risk siblings, 262 low-risk siblings).

Measures

***Autism Diagnostic Observation Schedule* (ADOS):[9]—**The ADOS is a standardized protocol that measures symptoms of ASD and has high inter-rater reliability and construct validity. It provides an overall total score (Social Affect + Restricted and Repetitive Behaviors) with empirically derived cutoffs for both autism spectrum and autism. A calibrated severity score, allowing comparison across modules, ranges from 1 to 10.[10] The ADOS was administered at both preschool (Modules 1 and 2) and school-aged assessments (Module 3) by clinical examiners trained to research-reliability standards who were unaware of previous diagnostic decisions.

Mullen Scales of Early Learning:[11]**—**This is a standardized developmental test for children birth to 68 months that provides T scores (mean=50, SD=10) for nonverbal cognitive, receptive and expressive language, and gross and fine motor skills. The Mullen scales have good internal consistency and test-retest reliability.

Vineland Adaptive Behavior Scales:[12]**—**This parent-report measure assesses social, communication, motor, and daily living skills. It is normed for use with infants to adults and provides standard scores and age equivalents. The Vineland was administered at all ages.

Social Communication Questionnaire **(SCQ):**[13]**—**This brief parent-report questionnaire assesses the same social, communication, and repetitive behavior symptoms of ASD as the longer parent interview, the Autism Diagnostic Interview-Revised (ADI-R). Initial studies[14] used a cutoff score of 15 as indicative of ASD but later investigations[14] established use of this instrument for children as young as age 2, using a lower cutoff of 11. The SCQ was completed by parents at both age 3 and school age. It was not administered at one site so these missing SCQ scores were estimated by transforming ADI-R total scores using linear regression.

Parent Concerns:[15]**—**At age 3, parents were asked whether they had concerns about their child's behavior or development. Responses were classified by coders trained to 80% reliability into one of seven categories of concern (social, language, repetitive behavior, motor, medical, temperament/behavior, regulatory). Primary variables of interest were total number of concerns and number of ASD-related concerns (a sum of social, language, and repetitive behavior concerns).

Preschool Outcome Classification: At the 3-year visit, participants were classified into one of three outcome groups, using an algorithm previously adopted for high-risk cohorts.[16] The Typical Development (TD) outcome group (n=462) did not meet criteria for ASD, had no more than one Mullen subtest 1.5 standard deviations below the mean, had no Mullen subtests 2 standard deviations below the mean, and had an ADOS score that was at least 3 points below the autism spectrum cutoff. The Non-TD group (n=185) was composed of children who did not meet DSM-IV criteria for ASD but had low Mullen scores (n=30) and/or elevated ADOS scores (n=72 within three points of the autism spectrum cutoff, n=83 at or above the autism spectrum cutoff). Obtaining an ADOS score over the autism spectrum cutoff was not sufficient for a diagnosis. Classification in the ASD group (n=99) required both an ADOS score at or above the autism spectrum cutoff and meeting DSM-IV diagnostic criteria for ASD, using all available data. Highly trained clinical researchers (e.g., licensed health professionals or research personnel with multiple years of experience in the ASD field) conducted the evaluations and determined outcome classifications.

School-Age Procedures: Participants were contacted and invited for an additional visit between 5 and 9 years of age (M=7.4 years, SD=1.4 years); over 80% of the sample agreed to participate and previously published analyses indicated no differences between those who were and were not followed at school age.[8,17] All were administered the ADOS Module 3, an IQ test (either an age-appropriate Wechsler scale, n=12, or the Differential Abilities Scale, n=2), the Vineland, and either the SCQ or the ADI-R. Outcome classifications used

DSM-5 diagnostic criteria and were conducted by experienced clinical researchers unaware of previous assessment results. Fourteen participants, who are the focus of the present paper, first met criteria for ASD *after* age 3 and had the diagnosis confirmed at their latest school-age visit (see Table S1, available online, for scores at mid-childhood). All sources of material collected at school age were used in making diagnoses, as is considered best practice.[18] Three of the 14 Late Diagnosed participants fell just shy of the ADOS cutoff, but met DSM-5 criteria based upon parent interview and other information collected (i.e., parent and examiner concerns, Vineland scores, SCQ or ADI-R scores; see Table S1, available online).

Results

Sample Characteristics at 3 Years

Table 1 displays descriptive statistics and assessment data for the Late Diagnosed group and the three comparison groups (ASD, TD, Non-TD) when they were 3 years old. The Late Diagnosed group had significantly lower ADOS severity scores than the ASD and Non-TD groups, but significantly higher ADOS severity scores than the TD group. The Late Diagnosed group demonstrated significantly higher Mullen scores than the ASD group and was not significantly different from the TD and Non-TD groups. On both the SCQ and the Vineland, the Late Diagnosed group had scores that did not differ from the Non-TD group but were significantly different from both the TD and ASD groups. Thus, in general, the Late Diagnosed group fell at an intermediate level between the ASD and TD groups. The one exception was in the area of parent concerns, in which the Late Diagnosed group had significantly higher total and ASD-related concerns than both the TD and Non-TD groups and did not differ from the ASD group. While the Late Diagnosed group contained a higher proportion of females than the ASD group, this difference was not statistically significant.

Our analytic plan included several methods to examine potential heterogeneity within the 3-year assessment data of the Late Diagnosed group. We hypothesized that group findings might obscure individual differences within the 14 cases and possible explanations for the later diagnosis.[6]

Algorithmic Outcome Classifications

The first method we employed to parse heterogeneity was the outcome classification based on Mullen and ADOS scores, described above.[16] Of the 14 children in the Late Diagnosed group, 9 had a TD outcome at 36 months, while 5 were classified as Non-TD, 3 due to elevated (but subclinical) ADOS scores, and 2 because they were over the ADOS cutoff but did not meet DSM criteria for ASD at 36 months.

Latent Class Analysis

The second method undertaken to understand phenotypic heterogeneity within the 14 Late Diagnosed cases was latent class analysis (LCA), conducted on the entire sample. We used the flexmix program in the R statistical package to conduct an LCA on 5 variables: ADOS severity scores, verbal and nonverbal mental age from the Mullen, SCQ total score, and

Vineland Adaptive Behavior Composite. The ADOS and SCQ scores were anchored at zero and modeled as Poisson distributions to accommodate the significant right skew of the data.

Results revealed no simple set of distinct classes in the data. The LCA found that up to 8 classes were distinguishable when using AIC or BIC values for best solution determination. We focused on the 3-, 4-, and 5-class solutions as the most interpretable from a clinical standpoint (Table S2, available online shows the cross-tabulation of outcome groups by LCA class membership). Regardless of which LCA solution was used, the Late Diagnosed cases were distributed across all classes, affirming heterogeneity within the group and failing to find a single pattern that explained the late diagnoses.

Table 2 provides descriptive statistics for the 4-class solution, as an example. Class 1 had scores in the average range of the Mullen and Vineland and ADOS and SCQ scores well below the ASD cutoff, so this class could be interpreted as the typically developing class. Class 2 was symptomatic across all measures and could be interpreted as the ASD class. Class 3 was in the average to high average range on developmental measures and low on ASD symptom measures, and was interpreted as a typically developing class of high function. Class 4 was somewhat affected on all measures, but below ASD cutoffs on the SCQ and ADOS, and was interpreted as a broader phenotype class.

Parent report vs. clinical assessment: Residuals analyses

One issue suggested by the LCA analysis, as well as by previous studies,[19] is that there may be a group of children with scores that are discrepant across the directly administered measures and the parent report instruments (i.e., where parents might report symptoms that were not apparent during clinical assessment, or vice versa). For example, in the 4-class solution in Table 3, the parent report scores (SCQ, Vineland) for Class 4 are relatively more average than clinical assessment scores (ADOS, Mullen). One hypothesis is that the Late Diagnosed cases were not identified at age 3 because evidence across measures was not consistent, decreasing clinician confidence in a diagnosis. To examine this possibility, we calculated residuals for each child when regressing ADOS severity scores on SCQ totals, where the residual was taken to be an indicator of the disagreement between parent report and clinical assessment. A similar analysis was done using Vineland and Mullen language domain scores. Table 3 shows the means and standard deviations of residuals for each of the outcome groups, where more highly positive numbers mean higher scores on the parent report measures versus the clinical assessment; smaller magnitude or negative scores indicate lower scores on parent-reported instruments than direct assessments.

On the SCQ vs. ADOS residual analysis, the Late Diagnosed group was marginally greater than zero (t=1.66, p=.10) and significantly greater than either the Non-TD or the TD groups (p<.05). The Late Diagnosed group was not different from the ASD group, however, indicating that parents in both groups reported relatively more symptoms on the SCQ than seen on the ADOS compared to the TD and Non-TD groups. For the Vineland vs. Mullen language scores, the Late Diagnosed group was not significantly different from any of the other three groups. Thus, the analyses of residuals did not point to a consistent pattern of discrepancies between parent report and directly administered measures as the reason the Late Diagnosed group was not identified at age 3. Similarly, Class 4 from the LCA, which

had the most discrepancies between parent report and directly administered measures, did not contain a disproportionate number of the Late Diagnosed participants. Residuals were actually largest for the ASD group, where the lack of alignment between parent report and direct assessment apparently did not influence the diagnostic outcome determinations.

Longitudinal change analyses

A final analysis of heterogeneity within the Late Diagnosed group focused on changes in their longitudinal phenotype from age 3 to the school-age visit. In each analysis above, a subgroup of the Late Diagnosed cases demonstrated typical or mostly typical development at36 months, despite meeting criteria for ASD in middle childhood. To examine change over time in autism symptoms, we constructed a harmonized variable that included all social, communication, and repetitive behavior items that are consistent across ADOS modules 1 and 2 (used at the 3-year visit) and module 3 (used at the school-age visit). This permitted an examination of change between preschool and middle childhood on items that can be scored across the full age range of our sample (i.e., symptoms which show developmental continuity). The items making up the harmonized composite can be found in Table S3 (available online).

We compared scores on the harmonized composite at age 3 and at the school-age visit. Seven of the 14 participants demonstrated a pattern in which ADOS scores significantly increased between age 3 and school age. The other seven participants had scores on the harmonized composite that were stable across time periods. Table 4 contains descriptive characteristics of these “Increase” and “Stable” subgroups at their 3-year assessment. The two subgroups had similar scores on the Mullen, Vineland, SCQ and Parent Concerns measures (all effect sizes in the small range; Cohen’s $d < .50$). The subgroups did differ significantly, however, on the ADOS, both the harmonized composite and the standard calibrated severity score, with the Stable subgroup demonstrating significantly higher scores than the Increase subgroup at age three.

Next, we performed an ADOS item analysis to examine whether there were particular patterns that were shared, as well as others that were distinct, between the two longitudinal change subgroups of the Late Diagnosed group. Means and standard errors for all ADOS items at the age 3 assessment were calculated for the Stable and Increase subgroups. Figure 1 includes the ASD, Non-TD, and TD groups for comparison. The gray area around the ASD, Non-TD, and TD group mean lines represents the 95% confidence interval. As can be seen, neither the Increase nor the Stable subgroup is within the ASD confidence interval on any ADOS item. Both subgroups have scores that are elevated above the TD group on several ADOS items (stereotyped words/phrases, pointing, response to name, initiating joint attention, and quality of social overtures). There is also divergence between the subgroups, with the Increase subgroup showing a typical pattern of scores at age 3 and the Stable subgroup a more atypical pattern on several items (e.g., echolalia, eye contact, showing, play, sensory, and hand mannerism items).

Finally, we examined whether there were differences in ADOS item patterns between the Increase and Stable subgroups in middle childhood. We explored whether some children do not show typical early red flags (e.g., deficits in joint attention, imitation, play) but only

more subtle features that are hard to detect and may not be measured in preschool (e.g., challenges with reciprocal conversation, empathy, circumscribed interests, etc.). Specifically, we examined whether the Increase subgroup showed a disproportionate number of these later-appearing symptoms that are only measured on the higher modules of the ADOS (items: Offers Information, Asks for Information, Reporting of Events, Empathy/Comments on Others' Emotions, Insight, Compulsions/Rituals) to see whether these symptoms account for the change and bring the participants up to diagnostic threshold. On the Module 3 items that are specific to later childhood and not scored in preschool, differences between the Increase (n=7, M=5.1, SD=1.7) and Stable (n=7, M=4.3, SD=1.6) subgroups were not statistically significant, $t(12)=0.98$, $p>.35$ and the effect size was moderate (d=.48), providing minimal support for this explanation.

Discussion

This study sought to explain why children who had undergone multiple comprehensive assessments, with known familial risk, and ASD as the primary outcome of interest, were determined to be ASD-negative in preschool, only to meet criteria when re-evaluated in middle childhood. Fourteen children, from three international autism research teams, were identified and compared to a large sample of high- and low-risk siblings from the same sites. The Late Diagnosed group fell in between the TD and ASD groups on most measures administered at age 3 and differed significantly from the ASD group on most variables. This indicates that there were real differences in their phenotypic presentation at age 3 from the early-diagnosed ASD cases and that the Late Diagnosed group did not simply represent clinical errors (i.e., "missed" cases). The one exception was on the parent concerns measure, in which the Late Diagnosed group had scores that were significantly higher than the TD and Non-TD groups and statistically equivalent to the ASD group. This is consistent with a recent study[19] reporting that parents of children with ASD may be able to detect clinically informative behaviors earlier than professionals and also consistent with our finding that parents in both the Late Diagnosed and the ASD groups reported more symptoms on the SCQ than were identified by standardized instruments like the ADOS.

Davidovitch and colleagues[6] described a group of children identified through a population-based registry who met criteria for ASD in school age after having been determined to not have ASD at earlier evaluations. They proposed four explanations for such delayed diagnoses: 1) diagnostic overshadowing from other conditions in the initial assessment, 2) emerging or increasing symptoms over time, 3) missed symptoms in the preschool evaluations, and 4) inaccurate diagnosis in school age. Closer inspection of our own data revealed significant heterogeneity within the early presentations of the Late Diagnosed participants. Using previously published algorithmic outcome definitions,[16] 9 of the 14 Late Diagnosed cases were classified as typically developing at age 3. Using a latent class approach, 8 of the 14 were classified into typically developing classes. Using a longitudinal approach, 7 of the 14 were in a subgroup that showed significant increases, from typical to ASD levels, in their ADOS scores between preschool and middle childhood. Five of the 14 children were classified in the "typical" subgroup at age 3 by all three methods.

Davidovitch et al.'s first explanation for delayed identification, diagnostic overshadowing, suggests that other developmental challenges may have been more prominent and obscured detection of ASD. Examining our data, 5 of the 14 cases fell into non-typical outcome groups using the algorithm outcome definition.[16] None of the 5 was formally diagnosed with another disorder, however. Exploration of clinical notes revealed examiner concerns about language, social reticence or shyness, and behavioral rigidity, which are more suggestive of subthreshold symptoms than overshadowing by another disorder. Thus, while Davidovitch's diagnostic overshadowing explanation is consistent with the age of identification literature, in which the presence of other disorders has been shown to lead to later diagnosis,[2,20] this pattern did not seem to fit any of our 14 cases.

Davidovitch et al.'s[7] second potential explanation for delayed diagnosis was late symptom onset, in which "the child's presentation changed or evolved, and ASD criteria were truly met at a later age after not having been present at an earlier age (p. 232)." This suggests that, in some children, the symptoms of ASD may not have fully emerged by 36 months. *A priori*, we expected few cases like this, since onset of ASD symptoms after age 3 has rarely been reported in the literature (other than children with childhood disintegrative disorder, who are generally much more affected and experience a catastrophic regression, unlike the present Late Diagnosed cases). One way we examined this possibility was by exploring changes in behaviors key to diagnosis (e.g., eye contact, gestures, directed vocalizations) that have developmental continuity and can be validly measured at all ages. Based on our longitudinal change analyses, 7 participants demonstrated statistically significant increases in their ADOS scores over time, from lower, non-ASD levels at age 3, which could be taken as evidence of just such an emerging phenotype over time. This conclusion was also supported by the analysis of individual ADOS item patterns (see Figure 1), which showed that the Increase subgroup had scores outside the ASD range on all items at age 3, even those measuring prototypic autism symptoms. Other studies have demonstrated that there appears to be a continuum of onset timing, with symptoms appearing and unfolding at different rates across children.[21,22] The 7 children in the current study who demonstrated marked changes in symptom presentation from preschool to school-age imply that there is not a critical age window (i.e., age 3) before which ASD-related features always are manifest, suggesting that such symptoms can continue to evolve after this age. This is consistent with the DSM-5,[23] which no longer includes an age of onset criterion for diagnosis and acknowledges that symptoms may not be fully manifest until "social demands exceed limited capacity" (p. 50).

Davidovitch et al.'s[6] third explanation is premised on under-diagnosis in preschool; that is, features of ASD were present but overlooked. This explanation is difficult to reconcile with the procedures used in the studies from which this data was drawn. All 14 children were seen at university autism centers, by clinical research teams with many years of expertise in early autism diagnosis, who performed multiple comprehensive ASD evaluations through age 3. What is more likely, we believe, is that some children (those in the Stable subgroup) demonstrated signs that were subthreshold at age 3 and did not evolve into impairment until environmental demands exceeded the child's abilities.[23] At age 3, the child may not have been quite outside the range of typical development in terms of social interest, communication, or behavioral rigidity, given the wide range of typical variation. But by school age, when these mildly atypical early features had not resolved, and information from

new social contexts revealed additional difficulties in social interaction, the behaviors were now judged by parents and clinicians as impairing and met diagnostic thresholds. This subgroup of 7 children might have had a more subtle presentation early in life, but some of the concerning behaviors do seem to have been present; they then intensified and came into sharper focus as more data from school and peer contexts accumulated. There was also a higher (but not statistically significant) proportion of girls in the Late Diagnosed group and most obtained Mullen scores in the average range at age 3. If examiners had the expectancy that girls or cognitively average children are less likely to have ASD, this may also have contributed to reduced clinician confidence at age 3 in some of these cases.

Davidovitch et al.'s fourth explanation is that ASD is over-diagnosed at later evaluations when parents seek out and push for a diagnosis to improve service provision. This possibility cannot be completely refuted with the current study design, but we believe it is more likely to apply to a clinically referred sample[6] than to a prospective sample. These authors[6] also noted a "lack of reliance on formal assessments" for the later visits in which the diagnosis was made, which was not applicable to the present study.

The current study explored two other explanations for delayed diagnosis. First was the possibility that measurement discrepancies (i.e., parent and examiner judgment) could lead to an initial reluctance to diagnose a symptomatic child and delay formal identification, but our data did not support this hypothesis. Second, we examined whether some children did not show typical early symptoms but only later-appearing features (e.g., deficits in reciprocal conversation, unusual interests, etc.) that are not measured on the ADOS in the modules used with preschoolers.[24] Perhaps some children have intact skills in the areas that the early modules of the ADOS focus on (e.g., joint attention, imitation, pretense) and deficits cannot be detected until instruments specifically designed to elicit the later-appearing signs are employed. Our data did not provide strong support for this explanation either.

A major limitation of this study is the small size of the Late Diagnosed group and therefore our findings must be interpreted with caution and require replication in larger samples. We cannot rule out retention biases, in which parents are more likely to return for a school-age visit because of lingering worries about their child. For this reason, it is not possible to estimate the prevalence of late diagnosis in high-risk children from the present data. Despite the small sample size, we conducted a number of *post hoc* tests to explore the behavioral phenotypes of the late diagnosed children, given the unique nature of this group and its potential ability to shed light on factors affecting age of identification. The present findings highlight the challenges of evaluating young at-risk children, who may present with a subtle phenotype early in life or show a prolonged time course of symptom development. Given the high-risk familial design of the current study, we do not know whether the results will generalize to low-risk groups, but the findings of Davidovitch and colleagues,[6] which inspired our work, suggest that subthreshold presentations and late-emerging symptoms are also seen in the general population. This emphasizes the need for screening and surveillance schedules that extend past 36 months and continued evaluation of any child who presents with atypical early development and/or high-risk status. Indeed, with age of ASD diagnosis remaining stubbornly at 4 years of age or later internationally,[1,2,25] despite apparent progress

in discerning early signs, understanding the early development of children diagnosed in the school-age years remains an important priority.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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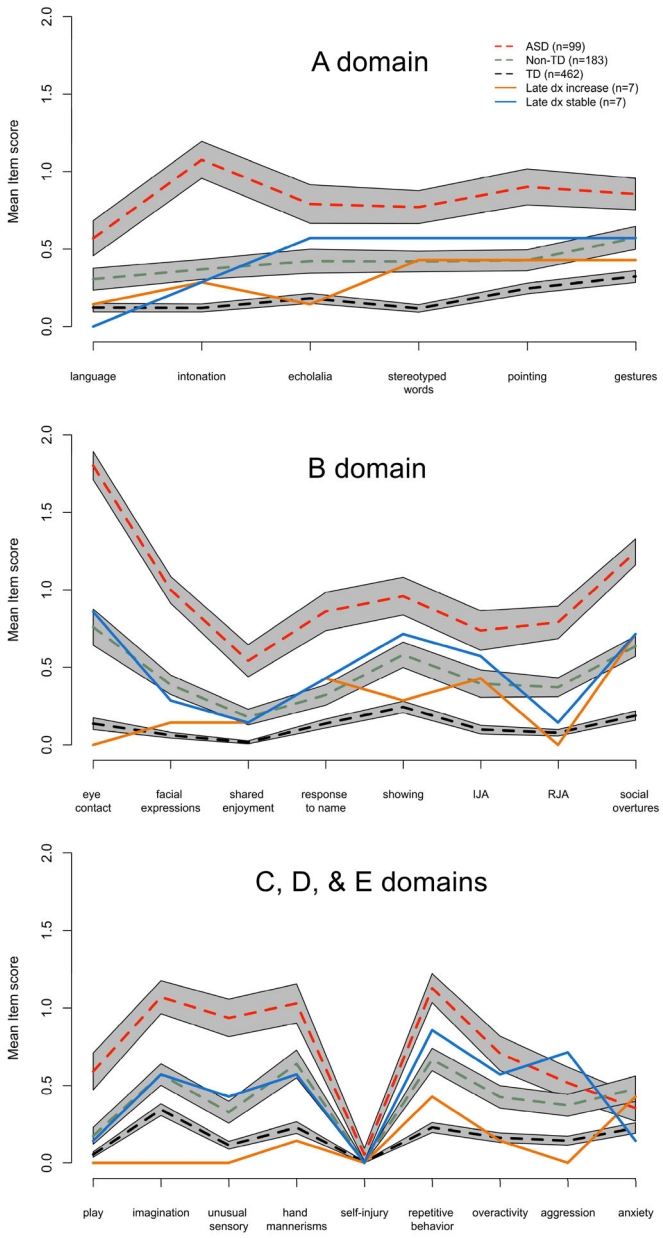

Figure 1: Means for All Autism Diagnostic Observation Schedule (ADOS) Items at Age 3 by Group.

Note: The gray areas around the ASD, Non-TD, and TD group mean lines represent the 95% CI. ASD = autism spectrum disorder; TD = typically developing.

Table 1:

Sample Characteristics at 3-Year Assessment.

	Late Diagnosed (n=14)	ASD (n=99)	Non-TD (n=180)	TD (n=453)
Age at 3-year visit (months)	37.28 (2.2)	38.18 (2.8)	38.10 (2.5)	37.61 (2.3)
Age at first visit (months)	6.86 (2.7)	8.23 (3.7)	7.18 (3.6)	7.20 (3.8)
Sex (percent male)	57.14%	73.74%	56.67%	47.02%
ADOS calibrated severity score	2.71 (1.9)	6.89 (1.7) ***	4.06 (1.8) ***	1.29 (0.5) ***
Mullen Expressive Language Age Eq	42.29 (8.9)	30.74 (10.4) ***	37.82 (9.0) *	41.06 (7.1)
Mullen Receptive Language Age Eq	39.71 (6.0)	29.59 (11.5) ***	37.38 (8.9)	40.82 (7.4)
Mullen Fine Motor Age Eq	36.07 (4.9)	31.31 (7.7) *	36.38 (8.3)	39.07 (6.5)
Mullen Visual Reception Age Eq	43.29 (8.5)	33.83 (12.0) ***	41.14 (10.0)	44.94 (7.6)
SCQ total score	7.29 (5.9)	13.25 (6.4) ***	5.38 (4.6)	3.54 (2.7) ***
Vineland ABC	94.70 (12.7)	79.18 (13.1) ***	94.88 (13.2)	101.79 (13.1) *
Parent ASD Concerns[a]	1.10 (1.45)	1.29 (1.2)	0.50 (0.9) *	0.24 (0.6) ***
Parent Total Concerns[a]	2.90 (3.0)	2.27 (1.8)	1.04 (1.4) ***	0.61 (1.0) ***

ABC = Adaptive Behavior Composite; ADOS = Autism Diagnostic Observation Schedule; Age Eq = age equivalent; ASD = autism spectrum disorder; ASD = autism spectrum disorder; SCQ = Social Communication Questionnaire; TD = typically developing

[a]Sample sizes for this variable: TD=302; Non-TD=144; ASD=48; Late Diagnosed =10

*p<.05;

**p<.01;

***p<.001; all comparisons made relative to Late Diagnosed Group

Table 2:

Characteristics of Latent Classes From the 4-Class Solution at 3-Year Outcome.

	Class 1 (n=274)	Class 2 (n=87)	Class 3 (n=229)	Class 4 (n=156)
Age at preschool outcome (months)	37.08 (1.6)	38.29 (2.9)	38.69 (2.9)	37.58 (2.3)
Age at first visit (months)	7.20 (3.7)	8.16 (4.2)	6.71 (3.1)	7.82 (3.9)
Sex (percent male)	52.92%	71.43%	38.43%	63.13%
ADOS calibrated severity score	1.37 (0.6)	5.55 (2.9)	1.90 (1.4)	4.46 (2.2)
Mullen Expressive Language Age Eq	37.80 (4.1)	32.15 (12.4)	46.93 (6.4)	33.60 (6.5)
Mullen Receptive Language Age Eq	37.16 (4.5)	31.89 (13.3)	47.02 (6.0)	32.76 (6.3)
Mullen Fine Motor Age Eq	36.22 (4.8)	32.47 (9.3)	43.86 (6.0)	32.78 (5.5)
Mullen Visual Reception Age Eq	42.48 (6.4)	35.40 (13.1)	49.89 (6.3)	36.42 (7.9)
SCQ total score	3.56 (2.1)	16.98 (5.0)	2.74 (2.0)	5.94 (2.9)
Vineland ABC	98.33 (8.9)	76.84 (13.5)	108.33 (10.5)	89.75 (10.9)

ABC = Adaptive Behavior Composite; ADOS = Autism Diagnostic Observation Schedule; Age Eq = age equivalent; SCQ = Social Communication Questionnaire; TD = Typically Developing

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Table 3:

Residual Analysis by Outcome Group.

	Late Diagnosed	ASD	Non-TD	TD
SCQ. vs. ADOS	1.81 (6.5)	2.98 (6.2)	−1.68 (5.1)*	−0.40 (2.7)*
Vineland vs. Mullen language	−1.71 (13.1)	−5.42 (9.7)	−0.85 (10.9)	1.87 (9.9)

ADOS = Autism Diagnostic Observation Schedule; ASD = autism spectrum disorder; SCQ = Social Communication Questionnaire; TD = typically developing

*p<.05; all comparisons made relative to Late Diagnosed Group.

Table 4:

Characteristics of the Longitudinal Change Subgroups at 3-Year Assessment.

	Late Diagnosed Stable (n=7)	Late Diagnosed Increase (n=7)
Age at 3-year assessment (months)	37.08 (1.7)	37.47 (2.8)
Age at first visit (months)	6.26 (3.2)	7.46 (2.3)
Sex (percent male)	71.43%	42.86%
Mullen Expressive Language Age Eq	43.29 (9.0)	41.29 (9.5)
Mullen Receptive Language Age Eq	39.71 (6.5)	39.71 (5.9)
Mullen Fine Motor Age Eq	36.29 (6.0)	35.86 (4.0)
Mullen Visual Reception Age Eq	44.14 (9.1)	42.43 (8.5)
SCQ total score	7.03 (6.3)	7.55 (6.0)
Vineland ABC	95.83 (8.3)	93.57 (16.6)
Parent ASD Concerns[a]	1.40 (1.7)	0.80 (1.3)
Parent Total Concerns[a]	3.60 (3.4)	2.20 (2.8)
N (%) with TD outcome at age 3	3 (42.9%)	6 (85.7%)
ADOS harmonized composite at 3	4.86 (2.0)	1.86 (1.1) **
ADOS calibrated severity score at 3	3.86 (2.0)	1.57 (0.8) *
ADOS harmonized composite at school-age	5.43 (1.7)	6.71 (1.4)
ADOS calibrated severity score at school-age	5.29 (2.5)	6.00 (1.4)

ABC = Adaptive Behavior Composite; ADOS = Autism Diagnostic Observation Schedule; Age Eq = age equivalent; ASD = autism spectrum disorder; SCQ = Social Communication Questionnaire; TD = typically developing

[a]Sample sizes for this variable: Stable subgroup = 5, Increase subgroup = 5

*p<.05;

**p<.01

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