Early Neurodevelopmental Trajectories for Autism Spectrum Disorder in Children Born Very Preterm

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abstract

BACKGROUND: Children born preterm are at high risk for autism spectrum disorder (ASD). However, there is still a lack of appropriate developmental markers. In this study, we aim to examine whether early mental performance trajectory is related to ASD outcome in the preterm population.

METHODS: The population-based cohort included 414 very preterm survivors born between 2008 and 2014. After excluding children with severe neurosensory impairment, 319 children with available records of developmental quotients before age 2 years were enrolled. The trajectory of mental performance evaluated by using the Bayley Scales of Infant Development across 6, 12, and 24 months of age was analyzed with group-based trajectory modeling. At 5 years of age, the ASD diagnosis was established by using the Autism Diagnostic Observation Schedule and the Autism Diagnostic Interview–Revised.

RESULTS: There were 29 children with ASD and 290 children without ASD. The mental performances from age 6 to 24 months could be classified into 3 trajectory patterns: low declining, high declining, and high stable, which corresponded to ASD prevalence at age 5 years of 35%, 9%, and 3%, respectively. ASD odds was 15 times higher in the low-declining group than in the high-stable group (odds ratio 15; 95% confidence interval 3.8–59; $P <$ .001). Through the analysis of multinomial logistic regression, we found that male infants with longer exposure to oxygen therapy whose mothers had lower maternal education levels tended to follow the low-declining trajectory.

CONCLUSIONS: The early-life mental trajectory patterns, by using the Bayley Scales of Infant Development, may lead to identification of vulnerable children born preterm for early ASD diagnosis and targeted intervention.

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WHAT'S KNOWN ON THIS SUBJECT: Early developmental trajectory is an indicator for autism spectrum disorder (ASD) in the general population. Preterm infants are at high risk of ASD. However, appropriate developmental markers at toddler age are still lacking.

WHAT THIS STUDY ADDS: In this population-based cohort, using group-based trajectory modeling, we found there are 3 patterns of mental performance trajectory for children born preterm from age 6 to 24 months, which is related to different susceptibility to ASD at age 5 years.

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Autism spectrum disorder (ASD) represents a spectrum of social communication deficits characterized by occurrence of restricted, repetitive behavioral patterns starting in early childhood.[1] Early diagnosis for early intervention is considered a crucial factor for good outcomes for ASD.[2] As the prevalence of ASD increases, it has raised concerns related to early detection through developmental surveillance in early life.[3,4] Children born preterm have recently been recognized to be at high risk for ASD.[5,6] However, several ASD screening tools, which are commonly administered in the general population, have failed to reveal accuracy in the preterm population at 18 to 36 months of age.[7–10] Hence, there is still a lack of appropriate developmental markers for early detection of ASD risk in toddlers who are born preterm.

In the term population, the developmental signature before 36 months of age is considered an early ASD marker.[11–14] An association between the neurodevelopmental trajectory and ASD risk has been validated in a general population cohort; however, this study did not include children born preterm.[15] Whether the early-life developmental trajectory contributes to the ASD risk in preterm populations remains unclear.

The Bayley Scales of Infant Development (BSID), which measures mental, language, and motor performance, is a widely used tool in the preterm population because of their high risk of neurodevelopmental impairment.[16,17] However, the relationship between the early neurodevelopmental trajectory patterns evaluated by using the BSID and the ASD diagnosis in the preterm population is unknown. Group-based trajectory modeling (GBTM) has been applied to capture the heterogeneity of trajectory within study populations and also to facilitate a causal inference.[18] Here, we used GBTM to examine the relationship between the longitudinal neurodevelopmental trajectory from age 6 to 24 months (assessed with the BSID) and the universal ASD outcome (measured with the Autism Diagnostic Interview–Revised [ADI-R] and the Autism Diagnostic Observation Schedule [ADOS]) at 5 years of age in the preterm population in south Taiwan.[19–25] We hypothesized that the mental performance trajectory patterns and the associated neonatal risk factors are useful to characterize the early developmental markers of ASD in the preterm population.

METHODS

Participants

In total, 414 very preterm infants (birth weight <1500 g; gestational age <32 weeks) who survived to discharge from 2008 to 2014 from the 4 NICUs in medical centers of Tainan City in southern Taiwan were enrolled. The demographics, perinatal and neonatal risk factors, and morbidities were collected during the infants' hospitalization in the NICUs (Demographic Data and Risk Factors section of the Supplemental Information). After discharge, the very preterm survivors were longitudinally followed-up for neurodevelopmental status in a single outpatient clinic at the university hospital.

Among the 414 preterm survivors, 360 (87%) could be followed-up to age 5 years (Supplemental Fig 3). The demographics of the children who missed the follow-up are shown in Supplemental Table 4. After excluding the preterm children who had cerebral palsy (n = 24), hearing impairment (n = 5), or congenital malformation (n = 7) for the confounding effect of concomitant neurologic disorders, 324 children were used for analysis (Criteria of Exclusion section of the Supplemental Information).[26,27] This study was approved by the university hospital's institutional review board. For each subject, informed consent was obtained from the parents during the hospitalization and at the follow-up visit.

Neurodevelopment Assessment at Age 6, 12, and 24 Months

At the follow-ups at 6, 12, and 24 months' corrected age, child psychologists evaluated the children's neurodevelopment using the Bayley Scales of Infant Development, Second Edition (BSID-II) for children born before 2011 and the Bayley Scales of Infant and Toddler Development, Third Edition (BSID-III) for those born after 2011. The BSID-II produces 2 composite scores: a mental developmental index (MDI) to assess cognition and language and a psychomotor developmental index for motor skills. The BSID-III has 3 composite scores: cognition, language, and motor function (BSID Scores section of the Supplemental Information). The cognition and language composite scores of the BSID-III were converted into the predicted MDI according to the algorithm proposed by Moore et al[28] for analysis. The predicted MDI converted from the BSID-III cognition and language scores, along with the MDI in the BSID-II, was used for a trajectory analysis to represent the mental performance of these preterm children.

Assessments of Cognitive Function and ASD at Age 5 Years

At age 5 years, cognitive function was evaluated by using the Wechsler Preschool and Primary Scale of Intelligence, Revised for children born before 2012 and the Wechsler Preschool and Primary Scale of Intelligence, Fourth Edition for those born after 2012. ASD diagnosis was made according to the *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition*, ADI-R, and ADOS, First Edition.[1,21,22] The team for the ASD evaluation was supervised by C.-H.C., an ASD specialist who received research training and research certification in the United States.[24,25] The psychologists performing the ADOS and the ADI-R were blinded to their previous neurodevelopmental scores. The diagnosis of ASD was established after

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a thorough discussion of the results of the diagnostic assessments by the team.

Module 3 of the ADOS was performed.[22] The cutoffs for ASD in the domains of communication and social interaction and the communication and social interaction total score were 2, 4, and 7, respectively. However, when interactions could not be elicited by tasks in module 3, examiners would use module 2 or 1 for appropriate evaluations. The ASD symptom severity was represented by the ADOS severity scores (including social-affect deficits, restricted, repetitive behaviors, and a total score), and the ADI-R scores included qualitative abnormalities in reciprocal social interaction (domain A); qualitative abnormalities in communication (domain B); restricted, repetitive, and stereotyped behavioral patterns (domain C); and abnormality in development evident at or before age 36 months (domain D) (The ADOS Severity Scores and the ADI-R Score section of the Supplemental Information).[21,22,29–31]

Statistical Analysis

Mental performance represented by the MDI from the BSID-II and the cognition and language scores from the BSID-III at age 6, 12, and 24 months were analyzed by using GBTM to classify homogeneous trajectory clusters without a priori assignment of ASD.[18,32] Fit criterion assessment plots were employed to select the best model fit for further analysis.[33] The Bayesian information criterion and the Akaike information criterion were used for model selection. Association of trajectory groups and ASD was analyzed by using a logistic regression with a Firth approximation.[34] A stepwise multinomial logistic regression was applied to select the important risk factors for the mental performance trajectories at an entry *P* value of .1 and a stay *P* value of .15.[35] Bootstrapping with 10 repeated samples was then used to compare the subsets of the selected variables by using the averaged Akaike information criterion and the Bayesian information criterion.[36] Risk factors were used to predict the attribution of trajectory groups by the multinomial logistic regression and multiclass receiver operating characteristic curves.[37] The association between the mental developmental trajectory groups with ASD was analyzed by using a multinomial logistic regression adjusted for the selected risk factors in the best fit model.[38] The 5-year-old cognition and ASD symptoms among the trajectory groups were compared by using the Kruskal-Wallis test and the Dunn's post hoc comparison. A statistical analysis was performed by using GraphPad Prism 5, SPSS software version 17.0 (SPSS Inc, Chicago, IL), SAS software version 9.2 (SAS Institute, Inc, Cary, NC), and the R project version 3.6.1.

RESULTS

Among the 324 children born preterm followed-up at 5 years of age, 30 were diagnosed with ASD and 294 did not have ASD. Serial BSID data from age 6 to 24 months were available in 319 children (BSID-II: *n* = 132; BSID-III: *n* = 187), including 29 children with ASD and 290 without ASD. The ADI-R and ADOS scores of the 29 children with ASD are shown in Supplemental Figs 4 and 5. Scores in domain D of the ADI-R revealed that 86% (25 of 29) of the children with ASD had ASD-related developmental problems at or before 36 months of age.

GBTM was used to examine the mental performance trajectory of these children across the period of 6 to 24 months. According to the Bayesian information criterion and the Akaike information criterion, a quadratic shape revealed a better fit (Supplemental Table 5). However, the model fits for the 3- and 4-group classifications were similar. For the purpose of the appropriateness of the estimated sample size, we selected the 3-group trajectory model for further analysis (Supplemental Table 6).

The 3-trajectory classification indicated the patterns of low-declining (*n* = 23; 7%), high-declining (*n* = 198; 62%), and high-stable (*n* = 98; 31%) mental performance dynamics (Fig 1). The high-stable group maintained normal and stable mental development across time, whereas both the low-declining and high-declining groups showed quadratic changes in mental performance with time. The 3 trajectory groups started at different intercepts at 6 months of age (high stable [93.8] > high declining [89.6] > low declining [72.7]). By 12 months of age, the low-declining group still had the worst mental performance (high stable [94.8] = high declining [90.3] > low declining [79.6]), but the mental scores of the high-declining and high-stable groups became indistinguishable. It was between age 12 and 24 months that the mental abilities of the high-declining and high-stable groups started to diverge. By 24 months of age, the high-stable group performed significantly better than the other 2 groups (high stable [96.9] > high declining [79.7] = low declining [59.1]).

The ASD prevalence rates revealed a gradient of changes across the 3 trajectory groups: as high as 35% in the low-declining group, 9% in the high-declining group, and 3% in the high-stable group (Fig 2). Compared with the high-stable group, the low-declining group had 15 times higher odds of ASD (odds ratio 15; 95% confidence interval [CI] 3.8–59; $P < .001$). The high-declining group also had a higher prevalence of ASD, although the odds did not reveal statistical differences (odds ratio 2.9; 95% CI 0.9–9.3; $P = .08$).

Among the 70 children whose 6-month mental scores were <85, 18 children exhibited improved mental scores >85, whereas the other 52 children did not by 24 months of age. None of the children with improved mental scores developed ASD at 5 years of age, in contrast to the 23%

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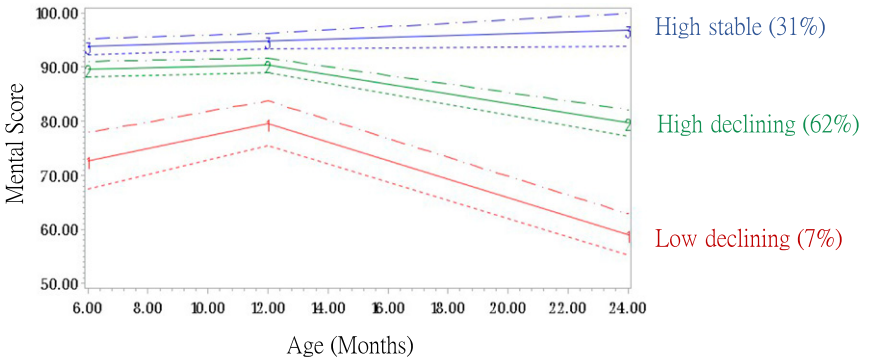

FIGURE 1

The trajectory patterns of mental performance from 6 to 24 months of age. The mental performance trajectory was classified into 3 trajectory groups: low-declining group (n = 23 [7%]), high-declining group (n = 198 [62%]), and high-stable group (n = 98 [31%]). The dotted lines represent 95% CIs.

(12 of 52) children without improvement who did develop ASD.

From the low-declining to high-declining group and up to the high-stable group, the children who showed inferior mental performance tended to comprise more boys and higher rates of lower gestational age, smaller birth weight, small for gestation age, and lower maternal education (Table 1). These children with lower mental performance were significantly more prone to have a longer duration on oxygen therapy, a higher rate of chronic lung disease, and a greater length of hospitalization. A multivariate regression with bootstrapping using stepwise selection revealed that 3 risk factors, sex, maternal educational status, and duration on oxygen therapy, significantly affected the patterns of mental trajectory that led to different rates of ASD at age 5 years (Table 2). As days on oxygen extended, the likelihood for the low-declining trajectory increased, whereas that for the high-stable trajectory decreased (Supplemental Fig 6). The area under the receiver operating characteristic curve was 0.74 by using the 3 risk factors to predict the development of the low-declining trajectory (Supplemental Fig 7).

A multinomial logistic regression model was used to elucidate the roles of the 3 risk factors associated with the mental performance trajectory from age 6 to 24 months and the occurrence of ASD at age 5 years (Table 3). After adjustment, maternal educational status and the duration on oxygen therapy became less significant to the odds of ASD, revealing that their mediations to ASD were dependent on the effects of

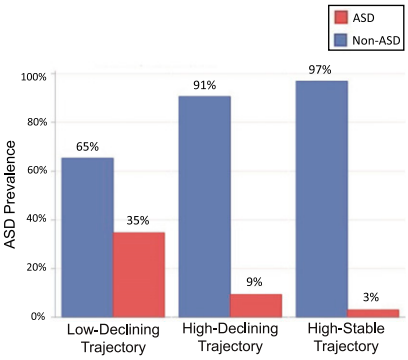

FIGURE 2

The ASD prevalence at age 5 years among the 3 mental performance trajectory groups across 6 to 24 months of age. ASD was most prevalent in the low-declining group (35%), followed by the high-declining group (9%) and the high-stable group (3%). The low-declining group had significantly higher odds of ASD than the high-stable group (odds ratio 15; 95% CI 3.8–59; $P < .001$).

TABLE 1 Differences in Demographic Data and Neonatal Morbidities Among the 3 Mental Performance Trajectory Groups

	Low-Declining Group (n = 23)	High-Declining Group (n = 198)	High-Stable Group (n = 98)
Demographics			
Male sex,[a] n (%)	18 (78)	112 (57)	38 (39)
Gestational age,[a] wk, mean (SD)	27 (3)	28 (2)	29 (2)
Birth wt,[a] g, mean (SD)	922 (235)	1076 (254)	1141 (225)
Maternal age, y, mean (SD)	31 (5)	32 (5)	32 (4)
Paternal age, y, mean (SD)	36 (7)	34 (5)	35 (4)
Maternal education, university and graduate school,[a] n (%)	5 (22)	60 (30)	43 (44)
Paternal education, university and graduate school, n (%)	8 (35)	79 (40)	43 (44)
Neonatal morbidities			
Small for gestational age,[a] n (%)	10 (44)	38 (19)	17 (17)
Intraventricular hemorrhage, grades 1 and 2, n (%)	2 (9)	34 (17)	24 (25)
Intraventricular hemorrhage, grades 3 and 4, n (%)	1 (4)	8 (4)	6 (6)
Cystic periventricular leukomalacia, n (%)	1 (4)	3 (2)	0 (0)
Hemodynamically significant patent ductus arteriosus,[b] n (%)	8 (35)	87 (44)	33 (34)
Blood culture–proven sepsis, n (%)	5 (22)	26 (13)	19 (19)
Necrotizing enterocolitis,[c] n (%)	2 (9)	12 (6)	4 (4)
Chronic lung disease,[a] n (%)	16 (70)	133 (67)	49 (50)
Retinopathy of prematurity,[d] n (%)	12 (52)	81 (41)	42 (43)
Steroids for chronic lung disease, n (%)	2 (9)	15 (8)	5 (5)
NSAIDs for patent ductus arteriosus, n (%)	7 (30)	87 (44)	31 (32)
Duration on oxygen therapy,[a] d, mean (SD)	63 (43)	44 (26)	35 (24)
Length of hospitalization,[a] d, mean (SD)	85 (36)	65 (25)	60 (22)

NSAID, nonsteroidal antiinflammatory drug.

[a] Differences with statistical significances among the 3 trajectory groups.

[b] Patent ductus arteriosus requiring medical or surgical treatments.

[c] Including stage IIA and above.

[d] Including stage I and above.

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TABLE 2 Multivariate Analysis of Demographics and Neonatal Morbidities on Trajectory Membership (the High-Stable Group Served as the Reference)

Risk Factors	Low-Declining Group			High-Declining Group		
	Odds Ratio	95% CI	*P*	Odds Ratio	95% CI	*P*
Male sex	7.3	2.2–24.3	.001	2.1	1.3–3.6	.004
Maternal education, university and graduate school	0.3	0.1–0.9	.03	0.5	0.3–0.8	.008
Duration on oxygen therapy, d	1.04	1.02–1.05	<.001	1.02	1.004–1.03	.006

the mental performance trajectory. In contrast, sex remained significant, suggesting its direct influence on ASD odds.

At age 5 years, the 3 mental trajectory groups had significant differences in mental capabilities and autistic behavior (Supplemental Table 7). Mental abilities, including general IQ, verbal communication skill, and visual spatial performance, varied among the 3 trajectory groups. In addition, the ADOS severity scores and ADI-R scores for ASD revealed that the low-declining group had significantly higher scores in every domain, indicating more severe autistic behaviors related to social communication and restricted, repetitive behaviors than in the other 2 groups.

DISCUSSION

We examined the ASD risk at 5 years of age in children born preterm with different mental trajectory patterns from age 6 to 24 months using BSID examinations. We found 3 distinct trajectory patterns, and the low-declining pattern was associated the highest ASD odds. The vulnerable trajectory pattern for ASD tended to be from male infants, with higher rates of lower maternal education levels and prolonged use of oxygen therapy. Our findings suggest that an early mental developmental trajectory is useful to characterize the differential risk for ASD outcome and that demographic and neonatal risk factors contribute to the trajectory, leading to higher ASD vulnerability.

The evolution of mental ability is better defined by longitudinal assessments than a cross-sectional evaluation.[39] In our study, we classified the mental performance trajectory of children born preterm from age 6 to 24 months using GBTM and then associated the trajectory pattern to the ASD odds at 5 years of age. Because the heterogeneity of mental development existed in both the children with ASD and the children without ASD, our results provided a different perspective on ASD susceptibility based on the dynamic patterns of neurodevelopment in preterm infants.

The BSID has been applied extensively in the preterm population.[16,17] However, corresponding the BSID results to future ASD susceptibility has not been reported. Because the validity of ASD screening tools has not yet been confirmed for the preterm population at toddler age, the mental performance trajectory provided by the BSID may give alerts to ASD concerns. Clinicians and parents may put emphasis on the behavioral aspect in the child born preterm who shows a consistently low or a declining mental trajectory.

The trajectory of early language and nonverbal cognitive development has been recognized as a risk indicator in term children.[11] Children with ASD exhibit slower acquisition of both verbal and nonverbal skills, leading to a dramatic decline in the composite IQ score during the second year of life.[11,12,14,15,40] However, the hypothesis has not been tested in children born preterm. Our finding of the association between mental performance trajectories and future ASD odds suggests that the early mental developmental trajectory may serve as a marker for ASD in preterm populations.

Early interventions to enhance person-environment fit is crucial to good outcomes in children with ASD.[2,41,42] The mental trajectory findings suggested that ASD can be suspected by 24 months of age. In addition, most children with ASD had evident developmental problems at or before 36 months of age according to our ADI-R scores. Taken together, our study indicates the possibility of ASD diagnosis at a younger age in preterm populations.

A study on term siblings with ASD revealed that the developmental trajectory of children with ASD began to deviate from 14 to 24 months of age.[12] The cognitive trajectory in a general population also identified

TABLE 3 Mediation Effects of Risk Factors on the Association Between Trajectory Classification and ASD

	Estimate	SE	Wald χ^2 Test	*P*	Odds Ratio	95% CI
Factors predicting ASD						
Low-declining trajectory[a]	2.5	0.8	9.8	.002	11.8	2.5–55.2
High-declining trajectory[a]	0.9	0.7	2.0	.2	2.5	0.7–9.0
Male sex	1.0	0.5	4.3	.04	2.8	1.1–7.3
Maternal education, university and graduate school	−0.2	0.4	0.1	.7	0.8	0.4–2.0
Duration on oxygen therapy	0.007	0.007	0.9	.3	1.007	0.993–1.021
Overall model	−4.1	0.8	28.4	<.001	—	—

—, not applicable.

[a] Compared with the high-stable group.

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a high risk of ASD in children with declining abilities after 12 months of age.[15,43] Our study revealed that preterm children with an ASD risk of 9% in the high-declining group were also characterized by a decline in mental performance between 12 and 24 months. The mental ability of the low-declining group, who showed the highest ASD prevalence of 35%, initiated from a significantly lower intercept at 6 months of age and continued to exhibit the worst scores at age 12 and 24 months. Hence, our study revealed that the differential time window for deviations in mental developmental carried different ASD risks in the preterm population: the children with atypical mental development in the first year of life had the highest ASD risk, whereas the children with a delay in mental development in the second year had an intermediate ASD risk.

Demographic and neonatal risk factors also interacted to affect the development of the trajectory pattern. We found that intrinsic factors and neonatal morbidities affected preterm infants' mental trajectory development. Using multinomial selection, we identified that male sex, prolonged oxygen exposure, and lower maternal education level had influential effects on the preterm infants, causing them to follow the low-declining mental trajectory.

Sex is known to play a significant role in outcomes in preterm populations.[44–49] We recognized that male sex was predictive of the trajectory of poorer mental performance and higher ASD odds. In addition, sex not only influenced the attribution of the mental developmental trajectory, which in turn brought about a distinct ASD risk, but also imposed a direct effect on ASD irrespective of cognitive function. These findings suggest the dual role of sex on ASD risk in children born preterm.

Ventilator support and chronic lung disease tend to increase cognitive impairment and ASD risk in preterm infants.[27,50–53] Preterm infants frequently require oxygen supplementation for respiratory insufficiency, but they are also vulnerable to oxidative stress because of immature antioxidant defenses.[54,55] In our study, we identified the effects of chronic lung disease and longer duration of oxygen therapy on mental performance trajectories and ASD risk, but the underlying mechanism affecting immature brain development remains unclear.[55]

The significance of maternal education is well-established in developmental psychopathology.[56–59] Our study revealed that higher maternal education exerted a protective effect on children's mental trajectory development against ASD risk. Maternal educational status may represent socioeconomical class, the quality of parenting skills, and also opportunities for cognitive stimulation at home.[60] The influence of maternal education highlights the importance of nurturing environments, apart from the physical issues, such as morbidities, associated with preterm birth.

In our cohort, 87% of children were managed for neurodevelopment from age 6 months to age 5 years. However, it is possible that the missing data in the remaining 13% of children could have affected the results.[18,32] Detailed family history and parent-child interaction patterns are needed for analysis of the genetic and environmental influences on ASD risk in children born preterm. Because extrauterine immature brain development is vulnerable to adverse exposures during critical care, further studies incorporating the clinical big data, as well as sophisticated neuroimaging analyses, may assist in predicting which trajectory an infant might follow for ASD outcome. Further multicenter studies recruiting more preterm infants for longitudinal neurodevelopmental follow-up and ASD diagnosis are necessary to validate our findings.

CONCLUSIONS

The current study revealed that early-life mental performance trajectory patterns by using the BSID for children born preterm were related to different susceptibility to ASD at age 5 years. The mental trajectory patterns may lead to early identification of vulnerable children for early ASD diagnosis and targeted intervention.

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ABBREVIATIONS

ADI-R: Autism Diagnostic Interview–Revised
ADOS: Autism Diagnostic Observation Schedule
ASD: autism spectrum disorder
BSID: Bayley Scales of Infant Development
BSID-II: Bayley Scales of Infant Development, Second Edition
BSID-III: Bayley Scales of Infant and Toddler Development, Third Edition
CI: confidence interval
GBTM: group-based trajectory modeling
MDI: mental developmental index

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Dr Chen designed and conducted the study, assisted in the statistical analysis, and drafted the manuscript; Dr S.-T. Wang performed the formal statistical analysis and drafted the manuscript; Drs L.-W. Wang and Kao conducted the study, assisted in the interpretation of data, and revised the manuscript for important intellectual content; Dr Chu conducted the study, interpreted the data, provided input on the data analysis, and revised the manuscript for important intellectual content; Dr Wu conducted the study, interpreted the data, and revised the manuscript for important intellectual content; Dr Chiang coordinated and supervised the conduction of the study, curated the data, and made critical manuscript revisions; Dr Huang conceptualized and designed the study, curated the data, and revised the manuscript; and all authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

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