Autism & Developmental Language Impairments
Volume 9: 1–13

DOI: 10.1177/23969415241286403
journals.sagepub.com/home/dli
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Early development score as a prognostic factor in nonverbal/minimally verbal children with autism spectrum disorder: A matched case-control study in Cyprus

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Abstract

Background and Aims: Children with autism spectrum disorder (ASD) present with impairments in social interaction and stereotypic behaviors. About a third may exhibit delays in verbal expression beyond preschool age, potentially categorizing them as nonverbal/minimally verbal (NV/MV), a condition that can persist into adulthood and affect their quality of life. The risk and prognostic factors associated with this reduced verbal outcome remain uncertain. This study aims to identify such factors within children diagnosed with ASD in Cyprus.

Methods: In this case-control study, 56 children aged 3–12 years, with an ASD diagnosis, participated. Among them, cases were 22 children classified as ASD-NV/MV, and controls were 34 children classified as verbal (ASD-V), matched by age group and gender. Retrospective information on familial, perinatal, and developmental risk and prognostic factors were collected to calculate the familial risk score (FRS), perinatal risk score (PRS), and developmental risk score (DRS). Early development information was collected for the Early Development Score (EDS) and Early Gesture Score (EGS), to measure the children's skill level as toddlers across milestones. A low EDS and/or low EGS reflected general developmental delays and decreased frequency of early gestures and were considered in the DRS. A parent report questionnaire was utilized to determine the current overall linguistic level and status of participants, distinguishing cases from controls.

Results: Age group and gender-matched cases and controls were similar in socioeconomic status and demographic characteristics ($p > .05$). Among the various familial (e.g., sibling with ASD), perinatal (e.g., prematurity), and developmental (e.g., ASD regression) factors examined individually, as well as collectively as scores in a conditional logistic regression (CLR) model, only a high DRS ($p = .03$), due to low EDS ($p = .04$) was significantly associated with linguistic status. When considering all risk scores in a multivariate CLR model, children with a high DRS were more likely to belong to the cases than to the control group ($p = .02$). In a subsequent model with low EDS and low EGS, only the low EDS was significantly associated with the case group. Results showed that children with ASD and a low EDS, reflecting general delays in early development, were 4.5 times more likely to belong to the cases group than those with a high EDS ($p = .02$).

Conclusions: Early developmental delays in developmental milestones across various domains like gesture, motor, play, linguistic, cognition, and joint attention, in toddlerhood, were associated with later decreased verbal outcomes. Children in the sample with such early delays (low EDS), had a higher likelihood of persistent language delays (ASD-NV/MV) even at late school age. Future studies are needed to duplicate findings and explore possible contributing factors affecting linguistic outcome in ASD through prospective studies exploring within ASD differences.

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Implications: These findings emphasized the importance of monitoring early development closely for children at risk for ASD, pre-diagnosis, to provide additional early support for those more likely to be ASD-NV/MV. Parents and specialists like pediatricians, educators, speech-language pathologists, among others, can track the EDS score of children at risk for ASD and refer to the appropriate specialists for early stimulation, intervention, and parent consultation promptly.

Keywords
Autism spectrum disorder, Cyprus, language development, minimally verbal children, prognosis

Introduction

Autism spectrum disorder (ASD) is a complex neurodevelopmental condition characterized by impaired social communication and repetitive behaviors according to the *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition* (DSM-5; American Psychiatric Association, 2013). Language skills can vary across the autism spectrum and affect opportunities for communication and interaction (Seretopoulos et al., 2020). A subgroup of individuals with ASD ranging from 19.0% to 36.4% (Armstrong & Jokel, 2012; Rose et al., 2016; Tager-Flusberg & Kasari, 2013) presents with absent or minimal verbal communication skills, which significantly impact their daily functioning and quality of life (Tager-Flusberg et al., 2009). It is important to note that language delays can persist for this subgroup of children with ASD, into adolescence and adulthood, regardless of the provided interventions. This substantial proportion of children with ASD highlights the considerable impact limited language abilities have within this population. Moreover, early language development in ASD was found to be a predictor of adult functioning (Magiati et al., 2014) and of scholastic or occupational attainment for children including those with ASD (Tager-Flusberg et al., 2011). Understanding the factors associated with a reduced verbal language level could be important for planning, interventions, and prognosis for these individuals. It could also provide insights into the underlying mechanisms of language impairment in ASD.

The definition of nonverbal or minimally verbal (NV/MV) children with ASD varied across studies (Tager-Flusberg & Kasari, 2013). Experts in the field have proposed utilizing a consistent developmental framework to define this subgroup, employing developmental language phases using various measures, such as, language samples, parent report tools, and tests (Tager-Flusberg et al., 2009). NV/MV language level refers to the absence or limited spoken language in individuals with ASD. This subgroup typically has difficulty combining words and thus using phrases and sentences or producing intelligible speech to effectively convey their needs, desires, and thoughts. They often rely on nonverbal communication methods such as gestures, pointing, or assistive devices, if trained to use them. To quantify their linguistic level, they may be either at the preverbal language phase (not yet using words) or at the first words phase, speaking in single words and not yet producing word combinations at phrase level speech (Tager-Flusberg et al., 2009).

Risk factors for ASD include familial genetic predispositions and perinatal factors, such as the use of medication during pregnancy, gestational hypertension, preeclampsia, and increased maternal age at birth, among others (Seretopoulos et al., 2020). Additionally, children with ASD have been found to have early motor delays compared with those without (Harris, 2017; Iverson et al., 2019). Although numerous studies have examined these familial and perinatal risk factors, and the developmental prognostic factors associated with an ASD diagnosis, very few studies have examined which risk and prognostic factors could be associated with linguistic skill variations within ASD. Bedford et al. (2015) found that early gross motor skills (e.g., the age a child started walking) reported by parents, were predictive of both language comprehension and verbal output, after controlling for cognition and autism symptom severity. Moreover, family history of ASD and male gender were considered risk factors for persistent language impairment irrespective of an ASD diagnosis, along with maternal education level as a measure of socioeconomic status (SES), and motor and gesture development (Tager-Flusberg, 2016). These factors need to be explored further within the population of children with ASD, to examine for possible associations with decreased linguistic outcome.

A systematic review of the literature concluded that early gesture was a significant predictor of later language outcome in ASD, in that those with limited use of gestures, had lower levels of language expression (Kilili-Lesta et al., 2022). Imitation and play were found to be associated with expressive language skills in a study of only NV/MV participants who were at least 5 years of age, and imitation was the only significant important concurrent predictor of language outcome (Pecukonis et al., 2019). The study did not compare children who were NV/MV to children with ASD who were verbal (ASD-V) and thus communicating with word combinations and at the sentence level. As the age of identification for ASD is decreasing, more early

developmental prognostic factors need to be explored than concurrent factors at a later age, so that early intervention can be optimized for this population. At the time of the ASD diagnosis, children might be diagnosed with comorbid language delay, however, little is known about their linguistic prognosis. A large proportion (60%–70%) of the children who would be considered NV/MV at preschool would improve their verbal skills above their NV/MV status (Mouga et al., 2019; Wodka et al., 2013; Yoder et al., 2014), but far fewer (35%–47%) would become fluently verbal by, or after school-age (Saul & Norbury, 2020; Wodka et al., 2013), while others would continue to be NV/MV.

It would be clinically useful to have the knowledge and resources to make a linguistic prognosis at the time of diagnosis, so that children who might have a higher probability of persistent language delay, be provided with a higher intensity or frequency of intervention, and even receive more personalized stimulation and additional support earlier than what is typically offered, to enhance their linguistic skills. Many times, pediatricians, parents, or educators follow a "wait-and-see" or "wait-and-evaluate-further" approach before referring for additional, or more intense services and valuable time might be lost (Edwards et al., 2021).

This study aimed to explore various risk and prognostic factors associated with prolonged language delay and thus NV/MV linguistic status in children with ASD in Cyprus. The factors examined would not only include those identified in the literature, such as gender, SES as measured by parent education level, family history of ASD, early gross motor, and early gesture development, but additional familial, perinatal risk, and developmental prognostic factors. This would be the first study to examine the association of numerous familial and perinatal risk factors, as well as developmental prognostic factors, on the linguistic outcomes of children with ASD. The study objectives included the analysis of factors individually, such as family history of ASD, prematurity, delay in walking/gross motor development, etc., and collectively as familial, perinatal, and developmental risk and ability scores.

Methods

Study Design

This was a matched case-control study that followed the Strengthening the Reporting of Observational Studies in Epidemiology (von Elm et al., 2014) guidelines. The case-control study design was chosen as the ideal approach to investigate the effects of risk factors in a population with a rare outcome (Song & Chung, 2010; Wan et al., 2021), such as children with ASD-NV/MV in a country with a small general population size of approximately 920.7 thousand people (Republic of Cyprus, 2021). Within the *National Autism Strategy* and *National Action Plan for Autism* between 2024–2028 in Cyprus the childhood ASD prervalence reported for the 2022–2023 school year, 1.8% of 5–12 year old children in schools (Kilili-Lesta et al., 2024). When the maximum global estimate (40%) of NV/MV status was applied to this prevalence rate, the population of interest for this study (ASD-NV/MV) was approximately 0.7% of the 66,126 student population (Press Release – NAS, 2024). Moreover, this study design allowed the examination of multiple risk factors for such rare outcomes. The cases in the study were matched to controls for the potential impact of sex/gender and age on the outcome, as these factors could act as confounders (Schulz & Grimes, 2002; Song & Chung, 2010). Additionally, age-matching helped to mitigate the increased potential for recall bias among parents of older children with ASD, compared to younger ones.

Study Population

The sample of the study comprised children aged 3–12 years with an existing ASD diagnosis by either child psychiatrists, child neurologists, or developmental pediatricians in the Republic of Cyprus. Children with severe motor and sensory impairments were excluded from the study. The children participated indirectly through parental report and were enrolled in schools where the language of instruction was Greek, thus systematically exposed to both standard Greek and the Cypriot Greek dialect.

Sampling and Sample Size

Convenience sampling was employed by inviting parents of children with ASD to participate in the study on behalf of their children through various channels, including their children's schools (only students with confirmed ASD diagnoses were invited), speech-language pathologists (SLPs), ASD associations, and the national ASD Family Intervention and Support Center (which exclusively admitted children with confirmed ASD diagnoses). The final sample consisted of 56 children, all of whom were diagnosed with ASD. The ASD diagnoses and linguistic status were independently confirmed by the researchers, for a portion of the sample (25%) who consented to provide medical certificates and allowed the collection and analysis of 10–20 min free-play language samples, by independent SLPs blind to the linguistic status of the children and the objectives of the study, as per the gold-standard method (Voniati et al., 2021) for the assessment of linguistic skill.

Data Collection and Study Instrument

The data were collected online between February 20, 2023 and November 20, 2023, utilizing the valid and reliable

Developmental/Verbal Language Phase (DeVLP) questionnaire, which collected the children's demographic, familial, perinatal, and developmental information. It was utilized to determine their current developmental language phase (DLP) and linguistic status (ASD-NV/MV, ASD-V), based on parent report. Parents responded to 45 closed-ended and multiple-choice questions, providing information mainly regarding sociodemographics (e.g., age, gender), school information (e.g., level, type), family background (e.g., parent educational level), perinatal conditions (e.g., pregnancy, labor type), early development (e.g., developmental milestones, early gestures), and overall current language phase.

The parents consented for their participation in the study, that the anonymous data collected about their children would be coded and kept offline by the main researcher in a password-protected hard-drive. For this reason, it was not possible to share the data in a public data repository. The data from the questionnaire yielded the current DLP (1–5) and linguistic level (ASD-NV/MV or ASD-V) of each child overall, separating them into two groups as displayed in Figure 1.

Cases and Controls

Those at DLP-1 (*preverbal*) and DLP-2 (*first words*) were considered as ASD-NV/MV based on the literature (Tager-Flusberg et al., 2009), and those at the higher developmental language phases (DLP-3–DLP-5) as ASD-V. Therefore, 34 children were included in the ASD-V group as controls and 22 in the ASD-NV/MV group as cases. Group membership was based on the overall language categorization by parents responding to the DeVLP questionnaire questions pertaining to the linguistic information.

The cases were matched with controls based on sex/gender (male and female) and age group, with the younger group aged at 3–5 years and the older group at 6–12 years. Participation was higher in the older age group, leading to a 1:1 case-to-control match for both genders in the younger age group, a 1:2 match for males, and a 1:3 match for females in the older age group.

Risk and Prognostic Score Calculations

Three risk scores per participant, namely the familial risk score (FRS), the perinatal risk score (PRS), and the developmental risk score (DRS), were derived based on parents' responses. The presence of a corresponding risk factor reported by parents earned 1 point, respectively. Thus, the risk scores were calculated by adding 1 point for each reported potential risk factor in each area, and a higher score represented higher risk. For the FRS, any reported family history of ASD and the presence of siblings with ASD were considered, for a total of 2 points maximum per child. Regarding the PRS, reported factors such as abnormal pregnancy, medication/hormone use during pregnancy, prematurity, cesarean labor, birth complications, low birth weight (< 2,500 g), and low APGAR score (< 7) were considered, for a total of 6 points per child. The DRS score included a point each for the presence of ASD regression, a low early development score (EDS), and a low early gesture score (EGS) for a maximum total of 3 points per child. For the 3 risk scores, those scoring above the middle-point of the maximum possible points were classified as high-risk (FRS ≥ 2, PRS ≥ 4, DRS ≥ 2).

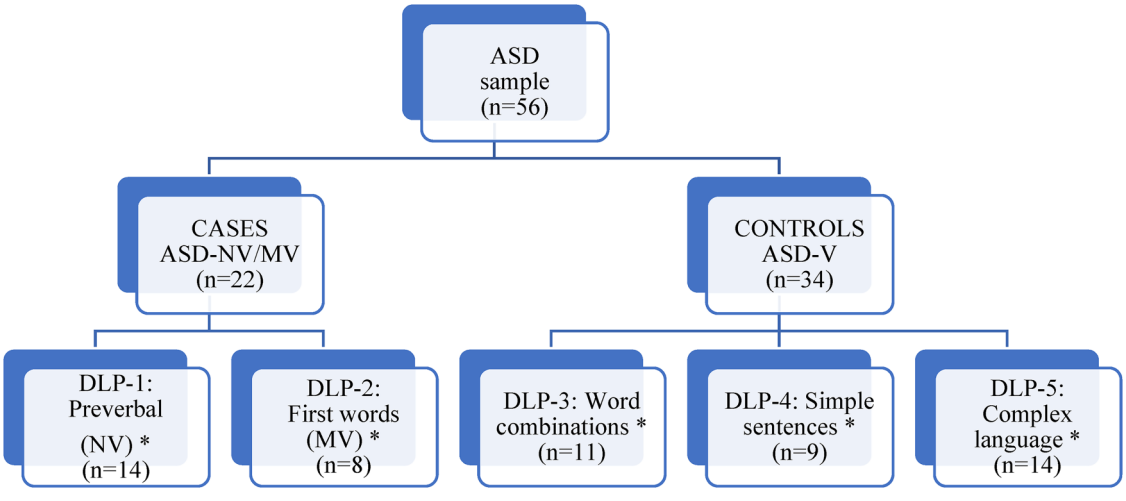

Figure 1. Flow chart displaying the process of determining cases and controls.
Note. DeVLP = developmental verbal language phase questionnaire; ASD = autism spectrum disorder; *n* = number; ASD-NV/MV = children with ASD who are nonverbal/minimally verbal; ASD-V = children with ASD who are verbal; NV = nonverbal; MV = minimally verbal; DLP = developmental language phase; * = based on results of the DeVLP questionnaire.

They were dichotomized based on the literature (Schulz & Grimes, 2002) to be able to determine the ratio of children exposed to each risk, compared to those not exposed for each group (Supplementary Figure 1).

The EDS and EGS, which comprised the DRS, were calculated by assigning points for skill level in each area, with a higher score indicating higher skill level. The EDS contained a total of 10 questions, with 3 focusing on gestures, 2 on motor skills, another 2 on play skills, and 1 each for joint attention, verbal, and cognitive skills. Timely mastery of each skill was awarded 2 points, delay was awarded 1 point, and no points were awarded if the skill was not yet attained. The maximum possible total for the EDS was 20 points per child. The EGS score included 11 questions regarding the frequency of gesture use for various gesture types, for example, pointing, etc., with the response "often use" being awarded 2 points, "sometimes use" 1 point, and "rarely use" without points, for a maximum total of 22 points per child. Those scoring below the middle-point of the maximum possible points were classified as low-skill ($EDS \leq 10$, $EGS \leq 11$). Therefore, a child would be considered as having a low EDS only if they were delayed in toddlerhood across all domains and milestones examined. Also, a child would be considered as having a low EGS only if they consistently had limited gesture use during toddlerhood reported as only "sometimes" or "rarely."

Statistical Analysis

Categorical characteristics (e.g., gender) were presented as absolute (n) and relative (%) frequencies, parametric numeric variables (e.g., age) as means (m) and standard deviations (SD), and nonparametric numeric variables (e.g., weight) as medians (Mdn) and interquartile ranges (IQR). The normality was examined using the Shapiro-Wilk normality test and QQ plots. Comparisons of the distribution of categorical variables (e.g., district) within and across groups (ASD-V and ASD-NV/MV) were conducted using the Pearson chi-square or Fisher's test accordingly, while the independent two-sample *t*-test or Mann–Whitney test were employed for numeric variables. Conditional logistic regression was applied to the matched case-control pairs, with stratification for age group and gender, as the most appropriate method for a low number of participants per stratum (Wan et al., 2021). Odds ratios (OR) were computed for each risk/prognostic factor both separately and collectively in binary (high/low) risk scores (FRS, PRS, DRS). Multivariate conditional logistic regression (CLR) was utilized to compare all the binary risk and prognostic scores together in one model. To ensure that the model requirements were met, covariate effects were examined, checks for separation were performed, and the Wald test was utilized as a goodness-of-fit test. The Benjamini–Hochberg procedure controlling the False Discovery Rate (FDR) was used to correct the regression models assessed for multiple testing. *P*-values less than .05 for two-sided statistical tests and 95% confidence intervals (CI) excluding 1.0 were considered statistically significant. In the case of the multivariate CLR models, *p*-values at or less than .02 were considered significant to adjust for the simultaneous examination of 2 or 3 factors. The R-Studio (version 4.0.3, RStudio Team, 2020) platform was used for data analysis.

Ethics

The Cyprus National Bioethics Committee (ΕΕΒΚ ΕΠ 2022.01.189) approved the study, which followed the ethical standards and regulations of the Helsinki Declaration for data privacy and confidentiality. All participants provided informed consent to be included in the study and anonymity for both the parents and the children was ensured.

Results

Fifty-six children diagnosed with ASD, participated in the study, with a mean age of 8.3 (SD = 2.7) years, predominantly male (78.6%) (Table 1). The majority (66.0%) received their ASD diagnosis between the ages of 2 and 4 years, resided primarily in the Nicosia district (75.0%), and lived in urban areas (71.4%). Half (50.0%) of the sample was born through cesarean section, most (62.5%) after a normal pregnancy, while around a fifth (21.4%) were premature. The median birth weight was 2,900 g (IQR = 2,589–3,180), with a median APGAR score of 9 (IQR = 9–10). Approximately a third of the children (37.5%) experienced skill regression, typically around 22 months of age. Common comorbidities reported included ADHD (35.7%) and DLD (28.6%). Only 7.1% of children were reported as having comorbid ID, all of whom belonged to the cases group. Most of the sample (71.4%) was also exposed to a language other than Greek or Cypriot Greek (e.g., Romanian, Russian, Arabic, etc.), with English being the most prevalent (46.4%), and only 28.6% grew up in monolingual households. All (100%) children attended public schools, half (50.0%) in primary schools, and only a few (14.3%) in special schools. About 39.3% were supported in the general education classroom with a school aide, 26.8% enrolled in a special unit, which is a classroom taught by a special educator, within a general education/mainstream school, and 19.6% were independent in the mainstream classroom. Approximately 70.0% of the sample had siblings, with only about 9.0% of them reported as also diagnosed with ASD. Respondents were mainly mothers (89.3%), married (87.5%), with at least a college degree (83.9%).

The sample comprised 2 groups: the ASD-V group, consisting of 34 (60.7%) children serving as controls, and the

Table 1. Comparison of children characteristics within overall sample and between verbal (ASD-V) and non/minimally verbal (ASD-NV/MV) subgroups.

	Child/parent characteristics	Overall ASD sample *n* (%)[a]	Controls ASD-V *n* (%)	Cases ASD-NV/MV *n* (%)	*p*
Overall sample	n (%)	56 (100.0)	34 (60.7)	22 (39.3)	.11
Age	m (SD)	8.3 (2.7)	8.5 (2.6)	8.0 (2.8)	.52
Age groups	3–5-year-olds	12 (21.4)[b]	6 (17.6)	6 (27.3)	.60
	6–12-year-olds	44 (78.6)[b]	28 (82.4)	16 (72.7)	
Gender	Male (M)	44 (78.6)[b]	26 (76.5)	18 (81.8)	.89
	Female (F)	12 (21.4)[b]	8 (23.5)	4 (18.2)	
	Ratio M:F	3.7	3.3	4.5	
Age of diagnosis	1–2 years	7 (12.5)[b]	4 (11.8)	3 (13.6)	.06
	2–3 years	19 (33.9)[b]	9 (26.5)	10 (45.5)	
	3–4 years	18 (32.1)[b]	10 (29.4)	8 (36.4)	
	4–5 years	3 (5.4)[b]	2 (5.9)	1 (4.5)	
	5 + years	9 (16.1)[b]	9 (26.4)	0 (0.0)	
Area	Urban	40 (71.4)[b]	26 (76.5)	14 (63.6)	.46
	Rural	16 (28.6)[b]	8 (23.5)	8 (36.4)	
District	Nicosia	42 (75.0)[b]	29 (85.3)	13 (59.1)	.06
	Limassol	4 (7.1)[b]	1 (2.9)	3 (13.6)	
	Larnaca	7 (12.5)[b]	3 (8.8)	4 (18.2)	
	Paphos	2 (3.6)[b]	0 (0.0)	2 (9.1)	
	Ammochostos	1 (1.8)[b]	1 (2.9)	0 (0.0)	
Pregnancy	Normal	35 (62.5)[b]	20 (58.9)	15 (68.2)	.83
	Premature	12 (21.4)[b]	7 (20.7)	5 (22.7)	
	Gestation diabetes	5 (8.9)[b]	3 (8.8)	2 (9.1)	
	Hypertension	1 (1.8)[b]	1 (2.9)	0 (0.0)	
	Overweight	1 (1.8)[b]	1 (2.9)	0 (0.0)	
	Placental abruption	1 (1.8)[b]	1 (2.9)	0 (0.0)	
	Preeclampsia	1 (1.8)[b]	1 (2.9)	0 (0.0)	
Labor type	Normal delivery	28 (50.0)	16 (47.1)	12 (54.5)	.78
	C-section	28 (50.0)	18 (52.9)	10 (45.5)	
APGAR score	Mdn (IQR)	9 (9–10)	9 (9–10)	9.5 (8–10)	.98
Birth weight (grams)	Mdn (IQR)	2,900	2,901	2,870	.70
	m (SD)	(2,589–3,180)	(423.2)	(2,550–3,130)	
ASD regression	Yes	21 (37.5)	11 (32.4)	10 (45.5)	.25
	No	32 (57.1)	23 (67.6)	9 (40.9)	
Regression age (months)	m (SD)	21.9 (9.3)	18.0 (18.0–23.0)	21.7 (11.1)	.82
	Mdn (IQR)				
Comorbidities[c]	ADHD	20 (35.7)[b]	12 (35.3)	8 (34.8)	.31
	DLD	16 (28.6)[b]	8 (23.5)	9 (39.1)	
	ID	4 (7.1)[b]	0 (0.0)	4 (17.4)	
	Other	4 (7.1)[b]	2 (5.9)	2 (8.7)	
	Mental disorder	3 (5.4)[b]	2 (5.9)	1 (4.3)	
	Genetic syndrome	2 (3.6)[b]	0 (0.0)	3 (12.0)	
	Epilepsy	2 (3.6)[b]	1 (2.9)	1 (4.3)	
	Hearing disability	1 (3.5)[b]	1 (2.9)	1 (4.3)	
	Vision disability	1 (1.8)[b]	1 (2.9)	0 (0.0)	
Language Exposure in addition to Greek/Cypriot Greek	English	26 (46.4)[b]	20 (58.8)	6 (27.3)	.29
	Romanian	4 (7.1)[b]	2 (5.9)	2 (9.1)	
	Russian	3 (5.4)[b]	3 (8.8)	0 (0.0)	
	Arabic	3 (5.4)[b]	2 (5.9)	1 (4.5)	
	Hungarian	1 (1.8)[b]	0 (0.0)	1 (4.5)	
	Spanish	1 (1.8)[b]	1 (2.9)	0 (0.0)	
	Georgean	1 (1.8)[b]	0 (0.0)	1 (4.5)	
	Filipino	1 (1.8)[b]	1 (2.9)	0 (0.0)	

(continued)

Table 1. Continued.

	Child/parent characteristics	Overall ASD sample *n* (%)[a]	Controls ASD-V *n* (%)	Cases ASD-NV/MV *n* (%)	*p*
School type	Public	56 (100)	34 (100.0)	22 (100.0)	.11
School level	Pre-primary	20 (35.7)[b]	11 (32.4)	9 (40.9)	**.01**
	Primary	28 (50.0)[b]	22 (64.7)	6 (27.3)	
	Special	8 (14.3)[b]	1 (2.9)	7 (31.8)	
School enrolment	General classroom	11 (19.6)	9 (26.5)	2 (8.7)	**.01**
	with aide	22 (39.3)	16 (47.1)	6 (27.3)	
	Special unit	15 (26.8)	8 (23.5)	7 (31.8)	
	Special team	8 (14.3)	1 (2.9)	7 (31.8)	
Family history	ASD	15 (26.8)[b]	8 (23.5)	7 (30.4)	.41
	ADHD	5 (8.9)[b]	4 (11.8)	1 (4.3)	
	DLD	1 (1.8)[b]	1 (2.9)	0 (0.0)	
Siblings	Yes	39 (69.6)	25 (73.5)	14 (63.6)	.37
	Twins (all fraternal)	4 (7.1)	3 (8.8)	1 (4.5)	.90
	With ASD	5 (8.9)	2 (5.9)	3 (13.6)	.65
	Younger[d]	1 (20.0)	0 (0.0)	1 (33.3)	.66
	Twin[d]	2 (40.0)	1 (50.0)	1 (33.3)	
	Older[d]	2 (40.0)	1 (50.0)	1 (33.4)	
Birth Order	First	26 (46.4)	15 (44.1)	11 (50.0)	.52
	Second	21 (37.5)	12 (35.3)	9 (40.9)	
	Third	9 (16.1)	7 (20.6)	2 (9.1)	
Parent's education level (SES)	Middle School	1 (1.8)[b]	1 (2.9)	0 (0.0)	.70
	High School	8 (14.3)[b]	4 (11.8)	4 (18.2)	
	Bachelor's	26 (46.4)[b]	15 (44.1)	11 (50.0)	
	Master's/PhD	21 (37.5)[b]	14 (41.2)	7 (31.8)	
Parent age	m (SD)	41.3 (5.0)	40.9 (5.2)	41.8 (4.6)	.49
Mother's age at birth	m (SD)	32.8 (4.8)	31.0 (29.0–34.0)	33.8 (4.3)	.05
	Mdn (IQR)				

Note. V = verbal; NV/MV = non/minimally verbal; *n* = absolute number; % = percentage; CI = confidence interval.
[a]Statistical significance considered vertically across categories (not across groups).
[b]Statistically significant within overall sample at $p < .05$, bold = statistically significant between subgroups; m = mean; SD = standard deviation; Mdn = median; IQR = interquartile range; ASD = autism spectrum disorder; ADHD = attention-deficit/hyperactivity disorder; DLD = developmental language disorder; SES = socioeconomic status.
[c]Percentage can be less or greater than 100%.
[d]Percentage of siblings with ASD.

ASD-NV/MV group, comprising 22 (39.3%) children as cases. These results are representative of the population based on the global findings in the literature, estimating that 30%–40% of children diagnosed with ASD are NV/MV (Tager-Flusberg & Kasari, 2013; Maltman et al., 2020). The groups in this study exhibited compatibility between them in demographic characteristics like SES ($p = .70$), area ($p = .46$), and district ($p = .06$), among other variables. However, they showed significant differences in school level ($p = .01$) and enrolment status ($p = .01$), directly related to their linguistic skills, which determined their group assignment. It was anticipated that children classified as ASD-NV/MV would exhibit moderate to severe difficulties and require more support compared to those classified as ASD-V. Only 2.9% of controls, as opposed to 31.8% of cases, were enrolled in special schools due to varying disability levels. While 26.5% of controls were independent in mainstream classrooms, only 8.7% of cases were able to participate without the support of a school aide. Despite about a third of participants experiencing developmental regression in their skills, their distribution was even across groups, without significant differences ($p = .25$), indicating that the presence of ASD regression was not associated with group membership.

A comparison of risk and prognostic factor scores across groups, independently, presented in Table 2, revealed a statistically significant difference only for the DRS as a continuous variable, as cases presented a significantly higher developmental risk compared to the controls ($p = .02$). This statistical difference was only reflected in the EDS ($p = .03$), but not the EGS ($p = .68$), compared as continuous variables. Children in the ASD-NV/MV group exhibited significantly lower total EDS compared to children in

Table 2. Comparison of DeVLP questionnaire scores within overall sample and between verbal (ASD-V) and non/minimally verbal (ASD-NV/MV) subgroups.

	DeVLP questionnaire scores	Sample overall ASD	Controls ASD-V	Cases ASD-NV/MV	*p*
Familial risk score (FRS)	Mdn (IQR)	0.0 (0.0–1.0)	0.0 (0.0–0.8)	0.0 (0.0–1.0)	.73
	Range	0.0–2.0	0.0–2.0	0.0–2.0	
Perinatal risk score (PRS)	Mdn (IQR)	1.0 (0.0–3.0)	1.5 (0.0–0.3)	1.0 (0.0–2.8)	.86
	Range	0.0–6.0	0.0–5.0	0.0–6.0	
Developmental risk score (DRS)	Mdn (IQR)	2.0 (1.0–2.0)	1.0 (1.0–2.0)	2.0 (2.0–2.0)	**.02**
	Range	0.0–3.0	0.0–3.0	0.0–3.0	
Early development score (EDS)	m (SD)	11.9 (4.3)	12.8 (4.3)	10.4 (3.8)	**.03**
	Range	0.0–20.0	0.0–20.0	3.0–20.0	
Early gesture score (EGS)	Mdn (IQR)/m (SD)	8.0 (4.0–13.5)	9.1 (6.2)	8.4 (6.4)	.68
	Range	0.0–22.0	0.0–22.0	0.0–22.0	

Note. DeVLP = developmental verbal language phase; ASD = autism spectrum disorder; V = verbal; NV/MV = non/minimally verbal; CI = confidence interval; m = mean; SD = standard deviation; Mdn = median; IQR = interquartile range; bold = statistically significant at $p < .05$.

the ASD-V group. Although no significant differences between the groups regarding age ($p = .52$), age group ($p = .60$), and gender ($p = .89$) were identified, it remained unclear how these factors could be associated with early development skills. Gender could be a moderating factor between early development level, age, and linguistic status. Matching the two linguistic groups by age group and gender was therefore applied, to assure that they were demographically similar. Additionally, the parents of children in the older age group had an increased probability of recall bias, compared to the younger age group, as the older children had more time to possibly overcome their developmental delays and thus be associated with a potential higher linguistic level. The enforced matching equalized this possible effect across groups.

The results of the CLR analysis, after stratification of cases and controls by age group and gender, were presented in Table 3. Multiple exposures were considered individually, including familial and perinatal risk factors, and developmental prognostic factors, such as early developmental milestones and early gesture use.

No difference was observed in the likelihood of children presenting with NV/MV status for any of the individually examined familial and perinatal risk factors, nor collectively as risk scores ($p > .05$). When the developmental prognostic factor of high DRS was investigated, it revealed a significant result, showing that children with ASD and a high DRS were five times more likely to belong to the cases, instead of the controls group ($p = .01$). The effect of a low EDS and low EGS was examined individually, revealing that only a low EDS was associated with later NV/MV linguistic status, regardless of age and gender. Children with a low EDS were four times more likely to belong to the cases (ASD-NV/MV) group, than those with a high score ($p = .02$). In contrast to the EGS, which focused solely on the frequency of gesture skills at 2 years of age (e.g., gesture repertoire, pointing, etc.), the EDS encompassed retrospective information on various domains, including gross-motor, fine-motor, joint attention, and linguistic, play, and gesture skills between 1 and 2 years of age. A low EDS score reflected a delay in achieving milestones such as joint attention, pointing, walking, and using first words at 12 months, building a tower with blocks, searching for hidden objects, pointing from a distance at 16 months, and playing symbolically, feeding themselves, and using various gestures up to 24 months of age. Delays in these early milestones were found to be associated with later decreased (NV/MV) linguistic status.

To determine the simultaneous effect of all risk and prognostic factors, the FRS, PRS, and DRS were entered collectively into a multivariate CLR model, as displayed in Table 4. A high DRS remained significantly different across groups, since children with a high DRS were 4.7 times more likely to be associated with lower linguistic outcome (NV/MV) than those with a low DRS ($p = .02$). Due to the inclusion of low EDS and low EGS in the DRS, these were simultaneously considered in a new multivariate CLR model, to establish which was most useful.

Results displayed in Table 5, revealed that again, only a low EDS was significantly associated with group differences ($p = .02$). A low EDS was significantly associated with decreased linguistic outcome (NV/MV) and children with early developmental delays had 4.5 times more probability of belonging to the cases than to the controls group ($p = .02$). Therefore, the significant difference in high DRS could possibly be mainly attributed to a low EDS, corresponding to general developmental delays during toddlerhood, rather than delays mainly in decreased repertoire and frequency of early gesture. The EDS score was fast to calculate because it required point calculation of only 10 responses per child. In contrast, the DRS was derived based on multiple responses in the questionnaire collecting familial, perinatal, and developmental information, which was more time-consuming than the EDS. In both multivariate CLR models, the significant variables

Table 3. Odds ratios for ASD-NV/MV linguistic status by risk, prognostic factors, and early skills scores, entered individually in the model.

Risk/prognostic variable	Status	OR	95% CI	*p*	Adj. *p* value
Individual variables					
Parent education (SES)	Low (no degree)	1.33	0.32–5.56	.70	.88
Age of diagnosis (years)	Early (≤3 years)	2.0	0.69–6.03	.19	.42
Family history of ASD [FRS]	Yes	1.5	0.46–4.77	.51	.73
Medication/hormone use during pregnancy[PRS]	Yes	0.9	0.24–3.63	.91	.91
Prematurity[PRS]	Yes	1.2	0.32–4.36	.81	.90
Birth complications[PRS]	Yes	7.9	0.84–74.72	.07	.40
Birth weight [PRS]	Low (<2,500 grades)	1.7	0.41–6.88	.47	.73
Mother's age at birth[PRS]	High (35+ years)	3.1	0.87–11.12	.08	.40
ASD regression [DRS]	Yes	2.6	0. 79–8.46	.12	0.40
Gross motor delay[EDS/DRS]	Yes	2.1	0.66–6.50	.21	.42
Collective scores					
Familial risk score (FRS)	High (≥2)	1.0	0.26–3.96	.98	.98
Perinatal risk score (PRS)	High (≥4)	3.3	0.55–19.94	.19	.29
Developmental risk score (DRS)	High (≥2)	5.0	1.44–17.46	**.01**	**.03**
Early development score (EDS)[DRS]	Low (≤10)	4.0	1.26–12.58	**.02**	**.04**
Early gesture score (EGS)[DRS]	Low (≤11)	1.3	0.40–4.34	.64	.64

Note. ASD = autism spectrum disorder; NV/MV = non/minimally verbal; OR = odds ratios; CI = confidence interval; Adj. = adjusted utilizing Benjamini-Hochberg correction; bold = statistically significant at $p < .05$; FRS = associated with Familial Risk Score; PRS = associated with Perinatal Risk Score; DRS = associated with developmental risk score; EDS/DRS = associated with the early development score within the DRS.

Table 4. Odds ratios for ASD-NV/MV linguistic status by simultaneous consideration of risk and prognostic factors.

Risk/prognostic variable	Status	OR	95% CI	*p*
Familial risk score (FRS)	High (≥2)	0.9	0.19–4.44	.92
Perinatal risk score (PRS)	High (≥4)	2.2	0.30–15.62	.44
Developmental risk score (DRS)	High (≥2)	4.7	1.30–16.70	**.02**

Note. ASD = autism spectrum disorder, NV/MV = nonverbal/minimally verbal; OR = odds ratio; CI = confidence interval; bold = statistically significant at $p < .05$.

Table 5. Odds ratios for ASD-NV/MV linguistic status by simultaneous consideration of sub-scores within the developmental risk score.

Binary Variables	Status	OR	95% CI	*p*
Early gesture score[DRS] (EGS)	Low (<12)	0.7	0.18–2.75	.61
Early development score[DRS] (EDS)	Low (<11)	4.5	1.28–16.18	**.02**

Note. ASD = autism spectrum disorder; NV/MV = nonverbal/minimally verbal; OR = odds ratio; CI = confidence interval; SES = socioeconomic status; DRS = part of the developmental risk score; bold = statistically significant at $p < .05$.

high DRS and low EDS remained significant after adjustment via the Bonferroni method, minimizing the risk for chance results.

Discussion

This study aimed to determine which risk and prognostic factors individually, or collectively as scores, would be associated with ASD-NV/MV status in children by comparing their exposure level on various familial, perinatal, and early developmental variables, to those with ASD-V status. Results showed that general developmental delays in toddlerhood, represented as exposure to high developmental risk (high DRS) and more specifically, low early development ability (low EDS) with delays in various developmental milestones, like walking, talking, pointing, playing symbolically, sharing attention, eye–hand coordination, and self-help skills among others, were associated with low linguistic verbal expression (ASD-NV/MV) in children, compared to those with a low DRS and a high EDS. The efficiency of collecting the information to measure the EDS through parents responses, by pediatricians, SLPs and others using a short section of the DeVLP questionnaire, was considered higher compared to collecting information for the DRS, rendering the EDS as favorable for use.

Currently, there is a lack of studies comparing variation in linguistic outcome within ASD. Unlike the results from a recent review (Kilili-Lesta et al., 2022), in the current study, the EGS was not significantly associated with linguistic status, despite its partial inclusion within the DRS. Interestingly, 30% of the responses required in the calculation of EDS, which was significantly associated with the case group, were specific to gestures. The main difference

between the EDS and the EGS was that the EDS identified a delay or absence of skill, whereas the EGS identified a possible reduced frequency of gesture use (e.g., "sometimes used," "rarely used"). The EDS therefore provided more developmentally rich information across various domains (e.g., gestural, verbal, gross motor, fine motor, etc.).

In a cohort study by Trembath et al. (2022), with 67 children with ASD identified at DLP 1–3, followed for approximately 7 months, only nonsignificant changes in DLP advancement were found for 13% of the sample. Of the rest, 82% remained at the same DLP within the NV/MV status and 4% regressed in their language skills. Seven factors considered simultaneously within a model, including age, language comprehension, ASD characteristics, symbolic word learning, and phonetic inventory among others, significantly predicted language change only collectively, not individually (Trembath et al., 2022). In the current study, although retrospective in nature, the factors associated with linguistic outcome, namely low EDS and high DRS, were significant both collectively and individually. Neither study controlled for the nonverbal cognition of participants.

Contrasting the design of the current study, the prospective nature of the Mouga et al. (2019) study allowed for the comparison of 3 groups, those who remained verbal, those who remained nonverbal, and those who became verbal. A significant difference was found in the age of diagnosis across groups, with the initially nonverbal groups becoming diagnosed earlier than the verbal group, revealing more severe ASD severity level. In the current study, no significant difference between groups on age of diagnosis was detected when utilizing retrospective information. However, findings in the current study were partly congruent with the results by Mouga et al. (2019) establishing that the neurodevelopmental profile of preschool children with ASD, as measured by early neurodevelopmental milestones in motor and verbal domains (e.g., onset of walking, first words, first phrases), predicted their later language output at school age. As in Mouga et al. (2019), no significant differences were found between groups regarding SES and gender, in the current study. However, it was not possible to control for nonverbal performance quotients in the current study. Another study found that male gender and SES were significantly different for ASD-NV/MV children (Maltman et al., 2020), unlike in the current study, despite SES measured similarly by parent education level, and agreement that low SES was considered for parents who did not gain a college/university degree. Moreover, in our sample, family history of ASD, male gender, SES, motor development alone, and early gesture alone, were not associated with later verbal outcome, contrasting the results of the study by Tager-Flusberg (2016).

In contrast to Bedford et al. (2015), in the current study early gross motor skill delays alone, as reported by parents, were not associated with later decreased verbal output. However, Bedford et al. (2015) controlled nonverbal cognition and symptom severity within the sample, while in the current study cases were matched to controls based solely on age and gender. The parents in the current study did not have consistent information to report regarding cognition level, since no protocol for measuring nonverbal IQ consistently was enforced. Only the parents of the children reported with comorbidity of ID (7.1% of the sample) were able to report it, as reported by the specialist within their child's diagnosis.

In a study of children with early communication delays at 9–18 months of age, who were later diagnosed with ASD at age 3, no significant differences were found in social communication skills when comparing those without language delay (ASD) to those with language delay (ASD + LD), who could be classified as NV/MV. Nevertheless, the researchers noted that they, like in the current study, did not control for nonverbal cognition at that age, which could be a predictive factor of verbal expression development (Delehanty et al., 2018). In their study, Delehanty et al. (2018) emphasized the importance of tracking early development for any potential delays in emotions, eye gaze, gestures, communication frequency, joint attention, word comprehension, and symbolic play.

This is one of a few studies identifying an early development measure to be associated with later verbal expression outcomes for children with ASD. Previous studies mostly examined the various developmental areas individually. In the current study, the allowance for various areas with emphasis on the gesture, motor, and play domains, to be combined into a single developmental score reflecting delay, opted for a low EDS score to be sensitive enough for an association with the linguistic level of children within the ASD sample. The current study highlights the importance of tracking early development (Delehanty et al., 2018; Mouga et al., 2019), both by parents and by other specialists providing services for infants and young children at risk for ASD and linguistic delay (e.g., pediatricians, educators, SLPs, etc.) well before a diagnosis is given. The factors causing these delays in these various areas remained unclear, nor was their effect on linguistic status. Nonverbal cognition could be a possible candidate, as it was found as the primary predictor determining which of the children who were ASD-NV/MV in preschool, became ASD-V by school age (Mouga et al., 2019). Even though the association of delays in early developmental milestones in various areas might not be exclusive to ASD, it could serve as a proxy for the prognosis of linguistic outcomes for newly diagnosed children with ASD (Mouga et al., 2019). The causal factors for ASD-NV/MV were outside the scope of the current study, but the results provide a basis for future research.

New research is needed both to replicate these results, and to delve into causality for developmental delays and their effect on linguistic expression in ASD. Future research could apply uniform nonverbal condition measures to the

sample and match cases to controls on this factor, in addition to age and gender, to examine whether a low EDS as reflected in a high DRS, would continue to be significantly associated with verbal outcome. Moreover, the EDS of children with ASD could be assessed as a predictor of later linguistic status overall and across different language domains (phonology, pragmatics, etc.), and as a screening measure for ASD-NV/MV to provide early enhanced communication intervention. Saul and Norbury (2020) found that the area of phonology and phonetics was an important predictor of increased verbal output in children identified as ASD-NV/MV. Those using more consonants and having more diverse phonetic inventories had shown improvement in language expression compared to those with poorer inventories (Saul & Norbury, 2020). Because the pervasive language delay exhibited in children with ASD-NV/MV was irrespective of provided treatment, future studies are needed to examine whether differences in the intensity and type of treatment provision between the ASD-V and ASD-NV/MV group would yield an effect in language outcome in the NV/MV group. Therefore, more intensive, and potentially more developmentally focused interventions for this group could be examined against the provision of existing intervention methods for the verbal group.

This study has limitations that warrant discussion. Causation cannot be inferred, and only associations could be discussed for the examined factors due to study design constraints. Although the study design is susceptible to recall bias overall, the possible increased effect for parents of older children with ASD, was equalized after matching based on age group. Children considered as ASD-NV/MV in the younger age group, between the ages of 3 and 5 years could potentially switch to the ASD-V group in the future. This limitation highlighted the importance of separating the age groups at 3–5 years for the younger and 6–12 years for the older age group and matching for this effect across groups. Additionally, the confirmation of the ASD diagnosis and linguistic status directly by the research team was only achieved for a subset of the sample. However, this was accomplished indirectly, as the associations, schools, and the family intervention center which served as pools for the sample, inviting parents to respond to the questionnaire of the study, only included children with confirmed diagnoses. On the positive side, the study demonstrated strengths in effectively matching cases with controls, ensuring similarity across groups, factors, and variables. Furthermore, the study design allowed for the comprehensive examination of multiple factors to identify associations with the outcomes.

Summary and Conclusions

Children with high developmental risk (DRS ≥ 2) in the sample presenting with delays as infants and toddlers in various domains (e.g., gesture, motor, play, linguistic, joint attention, etc.), receiving a low EDS ($\leq$10), had a higher likelihood of presenting with persistent language delays even after school age. This matched case-control study offered a unique opportunity to explore within-group differences among children with ASD in Cyprus concerning their current language outcome, a crucial predictor of functionality in adulthood, particularly during the preschool years. The identified association between delays in early developmental milestones at 1–2 years of age and limited verbal expression before 13 years of age, establishes a valuable foundation for future research. This foundation can aid in determining the potential causal relationships between these factors in future research and guide actions aimed at minimizing the proportion of NV/MV children with ASD. The vision is to maximize their potential for a more functional life during adolescence and adulthood.

Acknowledgments

We would like to thank all the parents and all children with ASD who participated in our study. We would also like to thank all schools, SLPs, ASD parent associations in Cyprus, and the Family Intervention and Support Center (AKTIdA) for forwarding our team's information-for-participation materials to parents whose children were diagnosed with ASD. We would not have a substantial sample size without their valuable support.

Author Contributions

Margarita Kilili-Lesta contributed to conceptualization. Margarita Kilili-Lesta, Konstantinos Giannakou, and Louiza Voniati contributed to methodology. Margarita Kilili-Lesta contributed to formal analysis and investigation. Margarita Kilili-Lesta contributed to writing–original draft preparation. Margarita Kilili-Lesta, Konstantinos Giannakou, and Louiza Voniati contributed to writing–review and editing. Margarita Kilili-Lesta contributed to visualization. Konstantinos Giannakou and Louiza Voniati contributed to supervision. All authors read and approved the final manuscript.

Declaration of Conflicting Interests

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Ethics Approval

The research study was approved by the Cyprus National Bioethics Committee (ΕΕΒΚ ΕΠ 2022.01.189). All participants provided their informed consent to participate in the study.

Funding

The authors received no financial support for the research, authorship, and/or publication of this article.

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Supplemental material

Supplemental material for this article is available online.

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