

# There are Gains, But can we Tell for Whom and Why? Predictors of Treatment Response Following Group Early Start Denver Model Intervention in Preschool - Aged Children with Autism Spectrum Disorder

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## Abstract

There is significant variability in treatment outcomes across different interventions for Autism Spectrum Disorder (ASD) and between individuals receiving the same intervention. This is likely related to the considerable phenotypic variability in ASD, which is posited to arise from a developmental cascade whereby a primary deficit in attention to social stimuli leads ultimately to widespread and diverse behavioural and functional difficulties.

**Purpose:** To provide data on predictors of treatment outcome in a cohort of preschool - aged children with ASD receiving a group Early Start Denver Model (ESDM) intervention.

**Methodology:** Forty-nine children (mean age 52 months) with ASD receiving group ESDM over 10 months were assessed pre - and post-intervention for ASD symptoms, developmental level, and adaptive functioning; together with measures of parental stress and coping.

**Results:** Lower initial ASD symptomatology, particularly higher social affect and play skills, and younger age at entry to intervention predicted better outcomes.

**Conclusion:** Reflective of hypotheses from the developmental cascade theory, younger age at entry predicted treatment gains, supporting efforts to include children in comprehensive treatment promptly. Moreover, greater initial social impairments led to relatively poorer outcomes, potentially suggesting that children with greater social affect difficulties may require a higher dose, or modified intervention, to that used in this study.

**Keywords:** Autism spectrum disorder; Early intensive behavioural intervention; Early Start Denver model; Communication; Receptive language

## Introduction

Autism Spectrum Disorder (ASD) is a life-long neurodevelopmental disorder estimated to affect around one in every 68 persons [1]. ASD is a disorder of significant public health importance that confers substantial personal, social and economic disadvantage. Due to its genetic and phenotypic heterogeneity, autism is generally viewed as a spectrum of conditions that affect individuals differently [2]. Some researchers have suggested that there are likely many 'autisms' with different underlying biological processes and developmental pathways [3]. In this regard, considerable genetic and clinical heterogeneity has been suggested with significant variations both in the etiological underpinnings and in the manifestations of the condition [4,5]. However, consistent with Kanner's original description, the core features include social and communication deficits as well as an 'insistence on sameness' [6].

## Developmental cascade model and treatment response variability

ASD has been hypothesised to result from a genetically determined developmental cascade of events whereby a primary deficit in attention to social stimuli leads to lack of social engagement with primary caregivers during infancy, resulting in reduced exposure to the reciprocal social interactions critical for healthy development of neuronal circuitry responsible for normal social behaviours as well as speech and language development [7-10]. Excitotoxicity and oxidative stress may in turn be underlying pathophysiological mechanisms that modulate the interaction between genetic, environmental as well as other risk factors [11]. The developmental cascade model suggests the importance of early intervention for ASD, in an attempt to maximise the brain plasticity, and is supported in part by studies showing better outcomes with earlier treatment, particularly using Early Intensive Behavioural Intervention (EIBI) [12-15].

While there is evidence to suggest better outcomes with EIBI when initiated early, there is considerable variation in response to treatment among children with ASD [16,17]. A systematic review of controlled studies of EIBI showed that, while EIBI resulted in improved outcomes for children with ASD compared to comparison cohorts at a group

level, there was marked variability in outcome at an individual level with around half the children making positive gains with the other half showing varying degrees of progress including little to no improvement. [18,19].

Variation in response to treatment is likely to be partly attributable to the inherent heterogeneity of ASD, and research aimed at developing methods for individualising treatment is important. Such research requires an understanding of the pre-treatment characteristics associated with differential response to treatment, including child and family variables, and how specific intervention techniques address each of these characteristics [19]. Warren et al., suggested the need for further investigation into predictors of treatment response to early intervention in ASD based on a systematic review, but to date there has only been limited research on individual differences linked to treatment outcomes [20,21]. A recent analysis of the literature noted that “the critical issue facing researchers, clinicians, and practitioners in the field is not as much a lack of evidence-based treatments, but rather an inability to predict which treatment will work best for each child” [22].

### Predictors of treatment response

Evidence from the available literature suggests that, in addition to age and severity of symptoms, individual child characteristics such as the level of intellectual functioning, communication and language level, adaptive functioning, as well as play skills including interest in functional use of objects, imitation skills, joint attention and engagement - are all potentially important in predicting treatment outcomes [12-15,18,23-47]. It is to be noted that there are also other studies that have failed to find associations between the above factors and response to treatment, suggesting a lack of generalizability of these findings, as well as the role of other factors including the dose effects, duration, quality, intensity and frequency of intervention [22]. The literature regarding predictors of treatment response was recently reviewed in a systematic analysis conducted by Howlin, Magiati, and Charman [18]. That analysis suggested that higher intellectual level and receptive language abilities were perhaps most strongly associated with degree of improvement, with this pattern found in four/five and four/seven studies, respectively. Stahmer et al., remind us that family and service-level factors are also important to consider in prediction of treatment outcomes [19].

The developmental cascade model provides hypotheses relevant to the prediction of treatment response. Specifically, given deficits in attention to social stimuli and social cognition skills are purported to reflect the core underlying deficit in children with ASD, it follows that the initial degree of difficulty a young person has in this area may be a key predictor of response to an ASD intervention, especially once other variables such as developmental level and age have been controlled for. Few studies have examined these social cognition and attention variables historically.

### Early Start Denver Model

An EIBI that is receiving increasing attention in the literature for pre-school children is the Early Start Denver Model, which has been found to be effective in a randomised controlled study setting as well as in a group-delivery model in the community setting [22,39,43,44]. Vivanti et al., also examined predictors of treatment response in their cohort of 21 children aged 2 to 5 years, finding that children with relatively better skills in the functional use of objects, goal

understanding and imitation made the best developmental gains after 1 year of treatment – whereas cognitive abilities, social attention, intensity of the treatment and chronological age were not associated with treatment gains.

### Study aims

The primary aim of the current study was to extend the literature on predictors of treatment response among preschool children receiving an EIBI, namely ESDM, delivered in a group setting. In selecting pre-intervention characteristics, particular weighting was given to social attention and cognition-related variables. Based on previous research findings, a variety of pre-intervention characteristics, including those related to general developmental level and child and family factors, were also selected as putative predictors of treatment response [21].

### Materials and Methods

#### Ethical approval

The study was approved by the Human Research Ethics Committees of the University of New South Wales and South Western Sydney Local Health District, and informed consent was obtained from all participating families.

#### Participants

Participants comprised 49 children who were attending an Autism Specific Early Learning and Care Centre (ASELCC) in metropolitan Sydney, Australia, which is one of six long day care centres established through funding from the Australian government to provide early intervention for pre-school aged children with ASD. In a previous publication, clinical outcomes of ESDM intervention in a subsample of 26 children were presented [4]. The current study involved a larger sample and focused on predictors of treatment response. All participating children had a DSM-IV-TR diagnosis of Autistic Disorder, made by a community-based physician, with the exception of one child with a diagnosis of Asperger’s Disorder and four children with a diagnosis of Pervasive Developmental Disorder Not Otherwise Specified. All of these children would have met DSM-5 criteria for a diagnosis of Autism Spectrum Disorder. Exclusion criteria were known neurodevelopmental (e.g., Fragile X Syndrome) or neurological (e.g., epilepsy) disorders, and significant vision, hearing, motor or physical problems.

The average age of children at the time of study commencement was 52 months (SD 6.5, range: 38 to 63 months) and 86% were male. The average age at which parents reported that they had become concerned about their child’s development was 21 months (SD 9.4, range: 0 to 46 months). English was the primary language spoken at home in 72% of families, although 65% of families reported a cultural background other than Australian. Two children were of Aboriginal or Torres Strait Islander background. Fifteen per cent of children lived in single-parent homes, while 85% lived with both parents. Twenty six per cent of participating children’s mothers had completed postgraduate education, 38% tertiary, 32% secondary, and 4% primary only. Data available on participating children’s fathers (n = 38) indicated that 16% had completed postgraduate education, 47% tertiary, 32% secondary and 5% primary only. Thirty one per cent of families reported an annual household income consistent with a low socio-economic status.

## Intervention

The study employed the previously published ESDM curriculum and teaching principles within a group setting [42]. The ESDM is a play based early intervention program that seeks to normalise the development of social and communicative capacities through provision of heavily enriched social stimuli by therapists and caregivers. In this study, a group delivery model of ESDM was used with children receiving 15 to 20 hours of group program with a 1:4 staff to child ratio, as well as two half-hour sessions of individualised intervention. Children were assessed using the ESDM-checklist and objectives for their treatment plan were derived as per each child's functional level. Behaviour coding was completed by the therapist after each activity and also by an independent scorer viewing a video of the session. All therapists were trained on the administration and scoring of the ESDM-checklist.

In order to be certified in direct delivery of this model, therapists were required to achieve

1) A fidelity rate of 80% or more with the ESDM trainer on each of the 13 ESDM teaching principles across multiple children and sessions, and

2) Same level of concordance on the individualised written treatment plans they had developed and data they collated on each child. That is, 80% or more concordance was required in both the clinical delivery and data recording aspects of the ESDM. There were six key workers, each trained in this way, involved in the study. Therapists also continued to receive clinical supervision in their delivery of ESDM by an accredited trainer.

## Measures

A range of measures were administered at two time points (on entry to the program, and again on exit or 12 months after entry, whichever occurred first). The mean length of intervention was 9.81 months (SD = 2.85). Parents also completed a demographic questionnaire on entry to the program.

## Autism symptoms

The Autism Diagnostic Observation Schedule (ADOS) is a semi-structured standardised observation that measures autism symptoms in social relatedness, communication, play, and repetitive behaviours [48]. The ADOS was conducted by staff with experience in administering the ADOS as a clinical tool. Depending on their expressive language ability upon entry to the study, children were administered either Module 1 (pre-verbal or single words) ( $n = 44$ ) or Module 2 (phrase speech) ( $n = 3$ ) of the ADOS. In the original scoring method, raw scores are converted into algorithm scores on four domains: Communication; Social Interaction; Play; and Stereotyped Behaviours. The ADOS algorithms were revised in 2007 to include the same number of items and similar content across Modules 1 to 3, in part to increase comparability and improve the interpretability of longitudinal comparisons across these modules [49]. The algorithm domain structure now includes a Social Affect domain and a Restricted, Repetitive Behaviour domain. The combined Social Affect and Restricted, Repetitive Behaviour score can then be converted into a Calibrated Severity Score, ranging from 1 to 10, in order to compare algorithm scores [50]. In order to facilitate comparisons across modules and time points for the purposes of the current study, revised algorithm and severity scores were therefore used [49,50]. Given that

play skills have previously been found to be a predictor of intervention response among children with ASD, and because of the theoretical importance of play skills in the ESDM, the original Play algorithm score was also used in the present study. In all cases higher scores denote greater ASD symptomatology.

The Social Communication Questionnaire (SCQ) is a 40-item parent-report dichotomous measure of autism-specific symptoms [51]. In addition to total scores, the SCQ also generates three subscale scores: Communication, Restricted Social Interaction, and Repetitive Behaviour. The SCQ has robust psychometric properties [52-54]. The first item of the SCQ assesses whether the child is able to talk using short phrases or sentences. This item is not scored, but determines whether the following six questions about speech are asked. Thus, if a parent answered 'yes' to the first item (i.e., his or her child is able to communicate verbally), all items are administered and scored, and total scores range from 0 to 39. Conversely, if a parent answered 'no' to the first item (i.e., his or her child is unable to communicate verbally), the following six questions are not administered or scored, and total scores range from 0 to 33. This scoring system is appropriate when using the SCQ as a clinical tool to inform possible diagnosis, but difficulties may emerge when using it for research purposes as there may be differing ranges of scores for verbal and non-verbal children. Therefore, for the present study, a value between 0 and 1 was calculated by dividing the total SCQ score by the number of items that had been answered (i.e., 33 for non-verbal children and 39 for verbal children) – giving the 'SCQ average item score'. The same process was used for calculation of subscale scores. For SCQ raw scores and SCQ average item scores, higher values are indicative of more ASD symptoms.

## Developmental skills

The Mullen Scales of Early Learning (MSEL) is a widely used, standardised measure of early development for children aged from birth to 68 months, yielding scores on the following subscales: Visual Reception, Receptive Language, Expressive Language, Fine Motor and Gross Motor [55]. The Gross Motor subscale was not administered in this study. Most children in the current cohort had low raw scores on the subscales making it difficult to calculate a T score that is meaningful. Hence we calculated standardised developmental quotients (DQs) whereby the age equivalent score on each of the MSEL subscales was divided by the chronological age and then multiplied by 100 [56]. An average of the four subscales was used to estimate an overall DQ to indicate the child's overall abilities and functioning. It was assumed that the child's DQ at two different time points would remain the same if the developmental trajectory of that child was stable even though the age equivalent score would have increased with the advancing age of the child. On the other hand, if the DQ increases at the second time point, that would be a reflection of improvement over and above the effects of age-related development and maturation.

## Adaptive functioning

The Vineland Adaptive Behaviour Scales – Second edition (VABS – II) assesses parents' perceptions of their child's everyday adaptive functioning in the domains of Communication (including expressive and receptive language), Daily Living Skills, Socialisation and Motor Skills [57]. For each domain, including an overall Adaptive Behaviour Composite, a norm-referenced standardised score with a mean of 100 and SD of 15 is calculated. Higher scores indicate greater levels of adaptive functioning. The VABS-II has well-established strong psychometric properties [57].

## Parental functioning

Parents completed two measures assessing their level of emotional functioning and sense of competence. The Depression Anxiety Stress Scales (DASS – 21) is a 21-item self-report measure that assesses negative affect, generating separate scores for the subscales of Depression, Anxiety and Stress [58]. Higher scores indicate greater symptomatology. The DASS-21 has been shown to have excellent psychometric properties [58-60].

The Parenting Sense of Competence Scale (PSOC) includes 17 items designed to measure parental self-efficacy [61]. The PSOC has been found to have strong psychometric properties [41]. Based on the factor structure found in Australian populations, the scale generates scores on three subscales: Satisfaction, Efficacy, and Interest, in addition to a total score, with higher scores indicative of higher levels of parental satisfaction and self-efficacy.

## Data analysis

Analyses were conducted using SPSS version 22 [60]. Alpha was set at 0.05 for all comparisons, following recommendations by Saville [62], who argues for this per-comparison level rather than a family-wise approach when conducting research in novel areas.

Cohen's d effect sizes were also reported. Following the recommendations of Dunlap et al. [63], and in order to provide a conservative estimate of the size of observed effects, Cohen's d scores were calculated using the pooled standard deviation uncorrected for the correlation between pre- and post-scores [63]. Dunlap et al., argue that, when pre-post scores are highly correlated, as was the case for several variables in this study, correction for the correlation results in a significant over-estimate of the true effect size [64]. It is widely

accepted that Cohen's d values  $\geq 0.2$  denote small effect size,  $\geq 0.5$  medium effect size and  $\geq 0.8$  denote large effect size. Bivariate correlations were performed to explore the association between change scores on outcome variables and baseline variables. When interpreting correlation coefficients, values of 0.1, 0.3, and 0.5 are taken to denote small, medium, and large effect sizes, respectively. Linear regressions were also conducted to further explore predictors of treatment response.

## Results

### Developmental gains and symptomatic change pre- to post-intervention

A series of paired samples t-tests were conducted to compare children's scores on the ADOS, SCQ, MSEL and VABS - II pre- and post intervention. As shown in Table 1, there was a significant reduction in average item scores (indicating a decrease in autism symptoms at a group level) for SCQ total; SCQ communication; and SCQ restricted social interaction from pre- to post-intervention. There was also a significant increase from pre- to post-intervention in the overall scores on the MSEL, which can be taken as a standardised index of the overall level of intellectual functioning. Further, there was significant improvement in Visual Reception and Receptive and Expressive Language scores on the respective subscales of the MSEL. Effect sizes tended to be small, however several, particularly those related to the SCQ, approached medium size.

	Time 1		Time 2					Standardised Change scores <sup>9</sup>		
	Mean	SD	Mean	SD	t	df	Cohen's d	Mean	SD	Range
<b>Social Communication Questionnaire</b>										
Total score <sup>a</sup>	0.55	0.18	0.46	0.2	3.04**	27	0.47	0.09	0.16	-0.71
Communication <sup>a</sup>	0.62	0.25	0.51	0.27	2.39*	27	0.42	0.11	0.23	-1.06
Restricted Social Interaction <sup>a</sup>	0.51	0.25	0.41	0.27	2.87**	27	0.39	0.1	0.18	-0.93
Repetitive Behaviour <sup>a</sup>	0.58	0.28	0.55	0.25	0.59	27	0.11	0.02	0.23	-0.96
<b>Autism Diagnostic Observation Schedule</b>										
Social Affect <sup>ab</sup>	14.72	4.35	13.44	4.75	1.91	24	0.28	1.35	3.54	-5.00 – 9.00
Restricted, Repetitive Behaviour <sup>ab</sup>	4.08	2.56	3.2	1.75	0.35	24	0.09	0	1.84	-4.00 – 4.00
Calibrated Severity Score <sup>c</sup>	7.46	1.72	6.92	1.86	1.54	23	0.33	0.4	1.7	-3.00 – 3.00
<b>Mullen Scales of Early Learning</b>										
Visual Reception DQ <sup>d</sup>	39.85	21.66	47	27.48	-2.53*	46	-0.29	7.16	19.44	-21.93 – 72.66
Fine Motor DQ <sup>d</sup>	45.92	20.46	49.46	21.5	-1.77	48	-0.17	3.54	14	-35.02 – 48.18
Receptive Language DQ <sup>d</sup>	27.29	20.11	33.41	22.83	-3.39**	45	-0.28	6.12	12.25	-14.41 – 38.76
Expressive Language DQ <sup>d</sup>	32.06	17.19	35.93	20.59	-2.58**	47	-0.2	3.87	10.37	-20.65 – 28.74
Overall MSEL DQ <sup>e</sup>	36.65	17.1	41.92	21.73	-3.54**	45	-0.27	5.27	10.1	-17.41 – 32.22



	Time 1		Time 2					Standardised Change scores <sup>g</sup>		
	Mean	SD	Mean	SD	t	df	Cohen's d	Mean	SD	Range
<b>Vineland Adaptive Function Scale</b>										
Communication <sup>f</sup>	61.6	12.9	62.04	20.14	-0.14	24	-0.02	0.44	15.3	-56.00 – 30.00
Socialisation <sup>f</sup>	67.5	11.43	63.41	18.01	1.29	21	0.28	-4.09	14.85	-57.00 – 26.00
Daily Living Skills <sup>f</sup>	65.29	11.83	61.04	18.34	1.49	23	0.29	-4.25	14.01	-52.00 – 27.00
Motor Skills <sup>f</sup>	72.04	16.91	70.22	17.56	0.46	22	0.1	-1.83	19.02	-67.00 – 20.00
Adaptive Behaviour Composite <sup>f</sup>	64.14	11.34	60.32	17.9	1.21	21	0.26	-3.82	14.76	-62.00 – 19.00

**Note:** \* p ≤ 0.05, \*\* p ≤ 0.01  
a. Higher scores indicative of greater symptoms of ASD  
b. Revised algorithm scores [49]  
c. Calibrated Severity Score [50]  
d. DQ = (age equivalent score/chronological age) X 100  
e. Overall MSEL DQ = (Visual Reception DQ + Fine Motor DQ+ Receptive Language DQ + Expressive Language DQ) / 4  
f. Standard score (mean: 100, SD: 15)  
g. Standardised such that in all cases positive values denote improvement and negative values denote deterioration Variability in Treatment Response

**Table 1:** Pre- to post-intervention and change scores for preschoolers treated with group ESDM.

Change scores were calculated and standardised so that positive change scores denoted improvements on all outcome variables (SCQ, ADOS, MSEL and VABS - II). For the MSEL and VABS-II, change scores were calculated by subtracting time 1 scores from time 2 scores, with positive change scores indicating improvements in developmental ability and adaptive functioning over the course of intervention. For the ADOS and SCQ, where higher scores denote more severe symptoms of autism, change scores were calculated by subtracting time 2 scores from time 1 scores, so that positive change scores would indicate a decrease in autism symptoms. Inspection of the standard deviation and range of change scores in Table 1 suggests that there was significant variation from pre- to post-intervention across participants. Although not statistically significant, deterioration at a group level was observed in adaptive skills across the course of the intervention, including overall adaptive behaviour, socialisation, daily living skills, and motor skills.

We note also that 57% of children had a MSEL DQ change score equal to or greater than 1 point, which could be considered an approximate index of overall treatment response.

**Relationship between baseline variables and change in developmental skills**

Response to treatment was operationalized as positive change scores on the key variables of developmental skills (MSEL), adaptive functioning (VABS - II), and autism symptoms (ADOS and SCQ). As discussed above, change scores were standardised so that positive values denoted an improvement in symptomatology on all variables over the course of the intervention. The set of baseline variables used in the analyses included the child’s chronological age, the age at which parents reported becoming concerned about his/her development, the duration of the intervention, developmental level (assessed with MSEL DQs), symptom severity across ASD domains (assessed with SCQ and ADOS scores), adaptive behaviour (assessed with VABS - II standardised domain scores), self-reported maternal wellbeing

(assessed with the DASS - 21) and perceived maternal parenting competence (assessed with the PSOC).

Pearson’s r correlations between baseline variables and change scores on the outcome variables were calculated. As shown in Table 2, baseline ADOS Social Affect, combined Social Affect and Restricted and Repetitive Behaviour, Calibrated Severity Score, and Play scores were significantly and negatively correlated with change in Visual Reception, Receptive Language and overall scores on the MSEL (i.e., greater baseline autism severity was associated with less improvement in developmental skills). Similarly, a significant negative association was found between baseline ADOS Social Affect and combined Social Affect and Restricted and Repetitive Behaviour and change in Expressive Language. These associations were of medium to large effect size.

There was also a significant negative correlation between chronological age and change in SCQ total scores and the SCQ Restricted Social Interaction subscale (i.e., younger age at entry to intervention was associated with greater reductions in autism severity) of medium effect size.

Significant positive correlations were observed between baseline Maternal Efficacy and total PSOC scores and change in ADOS Social Affect scores, and between baseline Maternal Interest scores and change in SCQ Repetitive Behaviour scores (i.e., higher perceived maternal competence at baseline was associated with greater reductions in autism severity) of medium-to-large effect size.

Finally, there were significant positive correlations between baseline ADOS combined Social Affect and Restricted and Repetitive Behaviour and Calibrated Severity Scores and change in motor skills as measured by the VABS - II (i.e., greater baseline autism severity was associated with greater improvement in motor skills) of medium effect size.

We note that baseline scores on several variables, including the MSEL, VABS - II and the DASS - 21, were not significantly correlated with change scores on any of the outcome variables. Further, there

were no significant correlations between the duration of the intervention or age at which parents first became concerned about their child's development and change scores on any of the outcome variables. Given the importance within the existing literature of intellectual and adaptive functioning to understanding treatment response in ASD, MSEL and VABS - II scores were nonetheless

included in subsequent regression analyses. Maternal Efficacy was also added to the regression equations seeking to predict change on ADOS variables. Duration of intervention; age at which parents first became concerned about their child's development; and measures of depression, anxiety and stress from the DASS - II were excluded from subsequent analysis, however.

	MSEL VR DQ change	MSEL RL DQ change	MSEL EL DQ change	MSEL Overall DQ change	ADOS Social Affect change	SCQ Total Score change	SCQ Restricted Social Interaction change	SCQ Repetitive Behaviour change	VABS-II Motor Skills change
<b>Chronological age</b>						-0.47*	-0.40*		
<b>Baseline Parental Sense of Competence Scale</b>									
Efficacy					0.56*				
Interest								0.44*	
Total					0.52*				
<b>Baseline Autism Diagnostic Observation Schedule</b>									
ADOS SA	-0.55**	-0.47**	-0.37*	-0.51**					
ADOS RRB									
ADOS SA + RRB	-0.48**	-0.49**	-0.35*	-0.51**					0.47*
ADOS CSS	-0.32*	-0.40**		-0.37*					0.46*
ADOS Play	-0.35*	-0.34*		-0.41**					
<p><b>Note:</b> * p ≤ 0.05, ** p ≤ 0.01. MSEL = Mullen Scales of Early Learning; VR = Visual Reception; RL = Receptive Language; EL = Expressive Language; ADOS SA = ADOS Social Affect; ADOS RRB = ADOS Restricted and Repetitive Behaviour; ADOS CSS = ADOS Calibrated Severity Score. Only significant correlations are presented. Correlations were not computed between baseline and change scores on the same measure.</p>									

**Table 2:** Correlations between baseline variables and outcome variable change scores<sup>a</sup>

### Predictors of treatment response

Linear regression analyses were conducted in order to further explore predictors of response to intervention. The following baseline predictors were included in all of the analyses: chronological age, MSEL overall DQ, SCQ total score, ADOS Social Affect and Restricted and Repetitive Behaviour, and VABS-II Adaptive Behaviour Composite. Given the theoretical importance of play skills in the ESDM, the ADOS Play algorithm was also included in the regression models, and as above, Maternal Efficacy was included in the regression equations where ADOS change scores were the outcome variables.

ADOS Social Affect and Restricted and Repetitive Behaviour scores were entered instead of the ADOS severity score, as the Calibrated Severity Score is adjusted for age and language and these variables were already accounted for in the regression models (chronological age and MSEL overall DQ).

Dependent variables included change scores on each of the outcome variables (MSEL, ADOS, SCQ and VABS - II). Results of these regression analyses, including standardised regression coefficients (beta) are presented in Table 3. Note that while a Bonferroni correction was not applied, as it happens, all values significant at the p ≤ 0.01 level would have remained significant were such a correction applied per outcome measure.

Mullen Scales of Early Learning change scores										
	Visual Reception		Fine Motor		Receptive Language		Expressive Language		Overall MSEL Score	
	$\beta$	p	$\beta$	p	$\beta$	p	$\beta$	p	$\beta$	p
Age	-0.16	0.37	0.06	0.76	-0.15	0.41	0.25	0.24	-0.04	0.82
SCQ total	0.1	0.68	0.21	0.45	-0.07	0.79	0.28	0.32	0.21	0.34
Social affect and RRB	-0.92	< 0.01**	-0.29	0.33	-0.8	< 0.01**	-0.61	0.05*	-1	< 0.01**
Play	0	0.99	-0.51	0.09	-0.16	0.54	0.12	0.68	-0.18	0.41
Adaptive behaviour	-0.49	0.09	-0.55	0.1	-0.64	0.03*	-0.08	0.82	-0.63	0.02*
Autism Diagnostic Observation Schedule change scores										
	Social Affect		RRB		Social Affect + RRB		Severity Score		Play	
	$\beta$	p	$\beta$	p	$\beta$	p	$\beta$	p	$\beta$	p
Age	0.15	0.59	-0.23	0.48	0.03	0.93	0.04	0.92	0.05	0.87
SCQ total	0.55	0.07	0.04	0.9	0.57	0.17	0.57	0.14	0.29	0.42
MSEL overall score	0.31	0.38	-1.4	0.01**	-0.39	0.42	-0.3	0.5	0.15	0.71
Adaptive behaviour	-0.39	0.28	1.35	0.01**	0.28	0.57	0.16	0.72	-0.52	0.27
Maternal Efficacy	0.97	< 0.01**	-0.45	0.12	0.74	0.04*	0.81	0.02*	0.5	0.07
Social Communication Questionnaire change scores										
	SCQ total		Communication		Restricted Social Interaction		Repetitive Behaviour			
	$\beta$	p	$\beta$	p	B	p	$\beta$	p		
Age	-0.62	0.01**	-0.13	0.64	-0.68	< 0.01**	-0.34	0.2		
MSEL overall score	-0.1	0.74	0.2	0.57	-0.41	0.14	-0.29	0.41		
Social affect and RRB	-0.64	0.03*	-0.55	0.11	-0.66	0.02*	-0.64	0.05		
Play	-0.07	0.82	0.12	0.36	-0.22	0.41	0	1		
Adaptive behaviour	-0.4	0.23	-0.32	0.42	-0.13	0.66	-0.15	0.69		
Vineland Adaptive Behaviour Composite change scores										
	Communication		Daily Living Skills		Socialisation		Motor Skills		Adaptive Behaviour	
	$\beta$	p	$\beta$	p	B	p	$\beta$	p	$\beta$	p
Age	0.55	0.84	0.13	0.63	0.72	0.8	0.37	0.14	0.41	0.08
SCQ total	0.03	0.92	-0.07	0.81	0.11	0.73	0.01	0.97	-0.09	0.71
MSEL overall score	-0.13	0.7	-0.11	0.73	-0.02	0.95	0.05	0.85	0	0.99
Social affect and RRB	0.4	0.25	0.48	0.18	0.65	0.06	0.85	0.02*	0.94	< 0.01**
Play	-0.55	0.12	-0.45	0.2	-0.69	0.06	-0.42	0.17	-0.57	0.04*
<b>Note:</b> * $p \leq 0.05$ , ** $p \leq 0.01$ . MSEL = Mullen Scales of Early Learning; RRB = Restricted and Repetitive Behaviour.										
a. Baseline and change scores on the same measure were not entered as independent and dependent variables into the same regression equation.										

**Table 3:** Predictors of change in development, adaptive behaviour and severity of autism symptoms<sup>a</sup>

MSEL scores as outcome variables: The baseline Social Affect and Restricted and Repetitive Behaviour score on the ADOS was a significant and negative predictor of a change in Visual Reception, Receptive Language, Expressive Language and overall score on the

MSEL after controlling for age, SCQ total score, play skills and overall adaptive behaviour (i.e., greater baseline autism severity was predictive of less improvement in developmental skills). Overall adaptive behaviour was a significant and positive predictor of change in Receptive Language and overall scores on the MSEL (i.e., lower levels of adaptive functioning at baseline were predictive of greater improvements in developmental skills), after controlling for other variables in the model.

**ADOS scores as outcome variables:** Change in Social Affect, Social Affect and Restricted and Repetitive Behaviour, and the Calibrated Severity Score were significantly and positively predicted by baseline Maternal Efficacy after controlling for other variables in the model. That is, mothers with greater perceived self-efficacy had children who went on to demonstrate relatively larger gains in these areas. In addition, change in Restricted Repetitive Behaviour was significantly and negatively predicted by baseline MSEL total score, and significantly and positively predicted by baseline adaptive behaviour. The direction of these relationships suggests that lower levels of developmental ability, but higher levels of adaptive behaviour, at baseline were predictive of greater reductions in autism severity.

**SCQ scores as outcome variables:** Age at entry to intervention was a significant and negative predictor of change in SCQ total score and the Restricted Social Interaction subscale score, after controlling for MSEL, ADOS and VABS-II indices (i.e., younger age at entry to intervention was associated with greater improvements in autism severity). Baseline Social Affect and Restricted Repetitive Behaviour was a significant and positive predictor of change in SCQ total scores, as well as change in the Restricted Social Interaction and Restricted Behaviour subscale scores, suggesting that lower levels of autism severity (as measured by the ADOS) at baseline were predictive of greater improvement in parent-reported autism severity (as measured by the SCQ).

**VABS-II scores as outcome variables:** After controlling for other variables in the regression model, baseline Social Affect and Restricted Repetitive Behaviour was a significant and positive predictors of change scores on Motor Skills and overall adaptive behaviour (i.e., more severe symptoms of autism at entry to intervention were associated with greater improvements in adaptive functioning). Baseline play skills were a significant negative predictor of change in overall adaptive behaviour (i.e., worse play skills at entry to intervention were associated with fewer improvements in overall adaptive functioning).

## Discussion

At a group level, children with ASD receiving an ESDM group intervention over a 10-month period were found to show reductions in ASD symptoms and make developmental gains over the course of the intervention. Notwithstanding these overall improvements, there was significant variability in individual response to treatment, consistent with previous research [18,19]. For example, while the current cohort as a whole was found to improve on overall MSEL DQ scores, 43% of participating children's scores on this variable were found to remain unchanged or decrease over the course of the intervention. This variability in treatment response underscores the importance of developing methods for individualising treatment for children with ASD, necessitating an understanding of the pre-treatment characteristics associated with differential response to treatment, a primary aim of the present study [19].

Regression analyses were run using key predictor variables based on previous literature: chronological age, autism severity, developmental level and adaptive functioning. Baseline ADOS Social Affect and Restricted and Repetitive Behaviour score emerged as a significant predictor of change in both developmental level and autism symptoms and the only common significant predictor across all outcomes measured. That is, less severe autism symptoms at entry to intervention were associated with greater improvement on Visual Reception, Receptive and Expressive language, and overall developmental skills on the MSEL; as well as greater reductions in parent-reported autism symptoms on the SCQ total score and the Restricted Social Interaction subscale. These findings are consistent with previous research demonstrating that a lower level of autism symptom scores at baseline is associated with improved EIBI outcomes [38]. The results of the preliminary correlations conducted in the present study suggest that these findings are driven by the Social Affect component of the ADOS, with the combination metric of Social Affect and Restricted and Repetitive Behaviour used in regression analyses largely for practical reasons. Better play skills at entry to intervention also predicted greater improvements in children's overall adaptive behaviour over the course of the intervention in regression analyses, and were associated with improvements in developmental abilities (Visual Reception, Receptive Language, and overall score on the MSEL) in correlational analyses. Previous research has demonstrated that play skills affect response to treatment among children with ASD, and these skills may be particularly important in predicting treatment response to the ESDM, which is a play-based intervention [28-31,42,65].

In terms of the reciprocal question regarding prediction of improvements in Social Affect, Maternal Efficacy emerged as a significant predictor, suggesting that higher perceived maternal self-efficacy at baseline was associated with greater reductions in autism severity. Significant positive correlations were also found between baselines maternal Interest scores and change in SCQ Repetitive Behaviour scores. Further research is warranted into possible mediators of this relationship, including parenting practices and implementation of the ESDM curriculum in the home setting.

Children's chronological age at entry to the intervention was also found to significantly predict change in total SCQ scores as well as change in the Restricted Social Interaction subscale, with younger children tending to show more improvement in parent-reported autism symptoms over the course of the intervention. This finding is consistent with research suggesting greater efficacy with entry into EIBI at the earliest possible age [16,66]. However, chronological age at entry was not associated with change scores on any other outcome variables in the present study. Similarly, age at intake was not associated with change in intellectual functioning, adaptive behaviour, or receptive or expressive language among children with ASD receiving a behavioural intervention, and Vivanti et al., found no association between age and improvements to developmental level or autism severity [25,39]. Perry et al., suggest that studies with wide age ranges that divide samples into younger versus older subgroups have typically found better outcomes in younger children, but that other studies, typically using correlational statistics, have failed to find such a relationship. They argue that small samples with restricted age ranges may preclude correlations from emerging as significant in these studies [33]. That observation may help to explain the absence of an association in the present study between chronological age and developmental and adaptive functioning outcomes. Indeed, the intake procedures from the service in which the current sample was recruited prioritises access for children in the year before they are due to start



primary school, which has somewhat limited the age range of this sample.

Unexpectedly, baseline developmental level was not associated with change in autism symptom severity or adaptive functioning – other than an isolated regression finding whereby lower developmental level predicted greater improvement in the Restricted Repetitive Behaviour subscale of the ADOS. This overall pattern is inconsistent with much previous research demonstrating a relationship between children's overall ability and their response to intervention for ASD. The relationship between children's social affect at entry and improvement in their autism symptoms, as well as the lack of observed relationship between baseline developmental level and reduction in autism severity, may be attributable to the fact that the ESDM intervention relies more on social-communicative skills rather than developmental ability, *per se*. Moreover, in the only study to date of predictors of outcome using the ESDM, Vivanti et al., did not find a significant relationship between baseline developmental level and change in autism severity [39]. It is conceivable that children with relatively higher levels of social affect may be suitable candidates for ESDM intervention, or that greater intensity of ESDM intervention may be required for children with relatively poorer social affect skills. One other possible explanation for the lack of observed relationship between baseline developmental level and treatment outcomes may be the potential "floor effect" brought about by the consistently low overall developmental level of participants in this cohort. In this regard, the range of developmental levels in evidence may not have afforded significant findings on this variable.

Some further unexpected findings emerged with respect to adaptive functioning. Firstly, there was a mean (although not statistically significant) decline in adaptive level across most areas assessed, including the adaptive behaviour composite – a result not observed for any of the other variables investigated. Other authors, including Dawson et al., have similarly found that adaptive level tends to remain constant with EIBI [42]. No significant correlations were observed between baseline adaptive functioning and change scores on any outcome variables; however, in regression analyses, once other variables were controlled for, baseline adaptive behaviour was found to significantly predict change in some outcome variables but the direction of these relationships was inconsistent. Better adaptive behaviour at baseline was predictive of a decline in developmental skills (Receptive Language and overall score on the MSEL) but an improvement in autism severity (Restricted Repetitive Behaviour on the ADOS). Further, more severe autism symptoms at entry to intervention (as measured by ADOS Social Affect and Restricted and Repetitive Behaviour score) was associated with greater improvements in adaptive skills (Motor Skills and overall adaptive behaviour), which is also an unexpected finding.

As discussed earlier, another study that specifically looked at predictors of treatment response to the ESDM in preschool children with ASD is that of Vivanti et al. While Vivanti et al., did not report an association between social attention (assessed using an experimental eye tracking task) and treatment gains, the present study found that social affect, assessed using the ADOS, was related to treatment gains [39]. The difference in findings between these two studies may be due to differences in the constructs and measures selected such as the use of experimental approaches versus clinical domain scores. Also, social affect, as measured by the ADOS, was used as a predictor variable in the present study but an outcome variable in the Vivanti study. Similarly, the present study did not specifically measure

functional use of objects, goal understanding and imitation, variables that were found to be related to treatment gains in the Vivanti et al study. It is conceivable, of course, that social affect, play skills, goal directedness and imitation skills are related constructs that combine to affect outcomes.

## Limitations

The relatively modest sample size employed in this research may have limited its power to detect predictive effects. Notwithstanding the logistical challenges involved, larger scale studies in this area would significantly advance the literature and allow stratification of data and the possibility of addressing the heterogeneity that so plagues the field. Further, the relatively broad measures used in this study and the use of several parent-report outcome measures, may ultimately be better replaced with more fine-grained and objective measures. Further, we suggest that the inclusion of a control cohort will strengthen future research.

## Conclusions

While there is significant variability, a majority of preschool-aged children with ASD show improvements following around one year of community-based ESDM intervention, and earlier age at entry to intervention as well as higher levels of baseline social affect and play skills appear to be related to improvements in developmental abilities and autism symptoms. It is unclear whether older children, and those with poorer social affect or play skills at baseline, may have benefited from a stronger 'dose' or perhaps different elements of intervention, and future work will need to bear this out, in addition to specific cut-offs for making such determinations. The findings of the study lend some support to the developmental cascade model with regard especially to severity of social awareness and cognition related variables providing the strongest prediction of change after intervention in this sample [7-10].

Based on our findings, and in conjunction with previous research, there is a strong case for ongoing research examining the variability in intervention outcomes in ASD. Notwithstanding the methodological variability in extant studies, a carefully constructed meta-analysis of the available literature would be invaluable in helping to align and direct future research studies.

The conflicting nature of research findings to date also highlights the limitations imposed by the tools we currently use to capture pre-treatment differences and individual variability present in ASD. Even when we do find that some variables, such as social affect, offer potential prognostic value, a question that follows is which aspects of social affect in particular are driving the observed findings? Finer grained measures of child characteristics, depending on the developmental stage of the child, are indicated, as findings are only as reliable as the tools that are used to measure the particular skill or domain, and the robustness of the theoretical model under which they are being applied. In this regard, the inconsistent findings in the literature on predictors of treatment response may partly be a reflection of the assessment measures used and the age of the cohort. For example, in toddlers, measures that would elicit precursors of language and social development including play, joint attention, and imitation may lend greater specificity to research findings [39].

More broadly, we note that there is a relative dearth of studies that utilise measures of neurocognitive functioning (e.g., neuroimaging or electrophysiology) or genetic subtyping as predictors of outcome in

ASD treatment and this will likely be an area of research focus into the future. Notwithstanding the heterogeneous nature of the disorder and the often conflicting findings in this research space, we remain hopeful that future work cognisant of the pitfalls inherent in this field will shed clinically meaningful light upon factors to consider when matching young people with ASD to treatments that are most likely to be effective for them [3]. Ultimately, longitudinal studies are critical to elucidate the long-term developmental trajectory of treatment outcomes in ASD and its determinants.

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