University of Modena and Reggio Emilia

PhD Program in Neurosciences

XXXV cycle

"*Which treatment for which child*?" Predictors of Response to a Naturalistic Developmental Behavioral Intervention in Children with Autism Spectrum Disorder

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Academic Year:
2021-2022

Abstract

Background: The effectiveness of early intensive interventions in young children diagnosed with ASD is now well established, but there continues to be great interindividual variability in treatment response. Furthermore, there is a need for parameters able to predict response to naturalistic developmental treatments, like the Early Start Denver Model (ESDM), as compared to more structured and therapist-driven Early Intensive Behavioral Interventions (EIBI). *Objectives:* The purpose of this study is twofold: (a) we performed a systematic review and meta-analysis of all published Literature to identify putative predictors of response to ESDM and EIBI; (b) we experimentally sought predictors of response in a sample of 32 children treated with ESDM for nine months after receiving an ASD diagnosis. *Methods:* (a) four databases (EmBase, PubMed, Scopus and WebOfScience) were systematically searched and quantitative, empirical studies published in peer-reviewed journals were included if ESDM or EIBI treatment were started between the ages of 12 and 48 months. Data were meta-analyzed combining p-values according to Fisher's method; (b) 32 children received 9 months of ESDM treatment each by a team of three certified therapists, four 90-min sessions/wk for nine months. A panel of tests was administered at the beginning (T0), after 4 months (T1) and at the end (T2) of treatment. *Results:* (a) our search yielded 1,601 articles, including 475 in WOS, 212 in PubMed, 666 in Scopus, and 248 in Embase. After study selection and the addition of eight studies found in the reference lists of selected articles, a total thirteen articles on EIBI and eleven articles on ESDM met the inclusion criteria. A set of socio-communication skills including intention to communicate, receptive and expressive language, and attention to faces, most consistently predicts response to ESDM (combined P=1.12E-11), while higher IQ/DQ at intake represents the strongest predictor of positive response to EIBI (P=8.24E-10). (b) Four children (13%) were full responders, 8 children (26%) were partial responders, and 20 children (61%) were low responders to ESDM. Strongest predictors of full response are joint attention (p = 0.002), the PEP-3 Cognitive Verbal and Preverbal scale (p = 0.003), and the GMDS-ER Personal-Social Scale (p = 0.007). PEP-3 Receptive Language (p = 0.03) and Visuo-Motor Imitation (p = 0.04) are significant predictor of partial/full response. *Conclusions:* Our systematic review and meta-analysis indicates that predictors of response to ESDM in very young children newly diagnosed with ASD tend to fall into the socio-communication and language domain, whereas response to EIBI seems to be better predicted by cognitive development. In line with this conceptual framework, our experimental study confirms that response to ESDM is associated with better socio-communication and

receptive language skills at treatment onset. Larger samples will be necessary to reach definitive conclusions, but this systematic review and our experimental findings begin to shed some light on patient characteristics predictive of preferential response to ESDM and to EIBI and may provide clinically useful information to begin personalizing treatment in very young children newly diagnosed with ASD.

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Chapter 1.
General Introduction

The term autism was coined in 1911 by the Swiss psychiatrist Eugen Bleuler to describe a severe case of schizophrenia, also a term he had coined a few years earlier. Bleuler believed that children with autism manifested excessive fantasies and hallucinations to avoid unsatisfying realities, and this idea was maintained for a few decades, until knowledge in the field of developmental psychology flourished, moving away from psychoanalytic theories (Evans, 2013). The term "autism" was then employed to refer to an opposite condition, namely the absence of symbolic inner life (*ibidem*).

The first Author to propose autism as an independent syndrome was the Austrian psychiatrist Leo Kanner. In 1943, Kanner published a description of 11 children, nine boys and three girls, whom he had observed in previous years and who displayed the same abnormal behaviors, though with some individual differences. These children were all characterized by an innate "inability to relate themselves in the ordinary way to people and situations" (Kanner, 1943; page 242), but not to objects. All but three had developed language skills, but it was employed literally, with an odd intonation, and not with the purpose of communication; furthermore, children exhibited monotonous and repetitive behaviors, such that every change in children's routine or environment "drove them to despair" (Kanner, 1943). Kanner claimed that these traits constituted a hitherto undescribed syndrome, possibly rare, resembling schizophrenia, though differing in that its characteristics were present from the beginning of life. He defined this condition an "inborn autistic disturbance of affective contact" (*ibidem*).

Since then, research on autism has proliferated, and yet it took almost 40 years to be officially recognized. Indeed, autism as a diagnostic category was included for the first time in Diagnostic and Statistical Manual of Mental Disorders, 3rd edition (DMS-III; APA, 1980) as Infantile Autism, a subclass of Pervasive Developmental Disorders. Afterwards, its label and definition have gone through several changes.

In the latest version of the DSM, the DSM-5 (APA, 2013), there has been a shift from a multi-categorical conceptualization of autism to a single diagnosis of Autism Spectrum Disorder (Rosen et al., 2021). This nomenclature now includes several conditions previously considered as separate disorders, such as Autistic Disorder, Pervasive Developmental Disorder Not Otherwise Specified, Asperger's Disorder and Childhood Disintegrative Disorder.

1.1 Autism Spectrum Disorder

1.1.1 Diagnostic criteria and epidemiology

Autism Spectrum Disorder (ASD) is a heterogeneous, life-long neurodevelopmental disorder characterized by persistent deficits in social communication and social interaction, repetitive behaviors, restricted interests or activities, and abnormal sensory processing (APA, 2013). According to the DSM-5, to receive an ASD diagnosis, symptoms must cause clinically significant impairment in relevant areas and must be present from early childhood. Commonly, core symptoms of ASD are recognized during the second year of life, but they can be noticed either before or after, depending on the severity of symptoms (APA, 2013).

Symptoms of other medical and/or psychiatric conditions are frequently reported in autistic people, more than in the general population (Lai et al., 2019). The most co-occurring disorders are attention-deficit hyperactivity disorder (ADHD; 28%), anxiety (13%), sleep disorders (12%), but also gastrointestinal disorders (30%) and epilepsy (20%) (Penzol et al., 2019; Lai et al., 2019; Reilly et al., 2014). Intellectual Disability (ID) occur on average in 33% of ASD cases (Zeidan et al., 2022), although some Authors believe that this rate may be underestimated because of the frequent under-inclusion of children with ID in ASD studies (Russell et al., 2019; Thurm et al., 2019).

Once thought to be a rare condition, with the first epidemiological research estimating a prevalence of 4.5 per 10 000 children (Lotter, 1966), currently autism affects 1-2% of the population in Western societies (Elsabaggh et al., 2012). In the last few years, we are witnessing a dramatic increase in diagnosis of ASD: suffice it to say that in 2012 the estimated overall median prevalence of this condition was 62 per 10 000 (Elsabaggh et al., 2012), while today this prevalence has increased to 100 per 10 000, although estimates vary considerably across regions (Zeidan et al., 2022). The reason for this upsurge is still under debate, and it remains unclear if it reflects a true increase in the frequency of ASD (APA, 2013), or whether this phenomenon can be ascribed to factors such as changes in diagnostic criteria, differences in study methodology, new diagnostic instruments, increased awareness in autism (see Matson & Kozlowski, 2011 for a review).

One factor that has remained stable over time is the higher incidence of autism in males than in females. According to recent estimates, the male-female ratio is about 4:1 (Zeidan et al., 2022). This gender imbalance is not limited to ASD but has been repeatedly observed in neurodevelopmental disorders. This has led several Authors to hypothesize a “female protective factor”, such that females would require increased etiological burden to manifest symptoms to the same degree of males (Jacquemont et al., 2014). Paradoxically, however, autistic females are more likely to present a more

severe phenotype. For instance, when taking into account autistic people with a comorbid moderate to severe ID, the male-female ratio decreases to 2:1 (*ibidem*).

This apparently more favorable clinical picture may lead to a failure in detecting autism among females. One study found that autism is less likely to be detected in girls than boys, especially if these girls do not display a comorbid ID, even when the severity of their symptoms are equal (Russel 2011). Furthermore, there is evidence that more women than men receive a diagnosis of ASD in adulthood (Happé et al., 2016), suggesting that they are not properly detected as autistic in younger age, contrary to their male peers (Hull et al., 2020). Some Authors believe that this may be due to a gender stereotyping, as this bias is not limited to ASD but also occurs in ADHD, another condition typically considered a male disorder, and more generally in the identification of children with special educational needs (*ibidem*).

1.1.2 The etiology of ASD

Causes of autism are still largely unknow. Nonetheless, epidemiological studies have shown that ASD is a highly inherited condition. A recent meta-analysis on twin studies estimated a heritability of 64-91%, with concordance of 98% for monozygotic twins and between 53 and 67% for dizygotic twins (Tick et al., 2016). Moreover, younger siblings of children already diagnosed with ASD have an 8.4-fold increase of being diagnosed in their turn, compared to the general population (Hansen et al., 2019). These results suggest an important genetic contribution to the etiology of ASD.

Hundreds of ASD risk genes loci have been identified in all human chromosomes (Genovese et al., 2020). Interestingly, a good amount of these genes is responsible for synaptic plasticity that are crucial in the developmental process of the brain and may thus represent potentially ASD-susceptibility genes (Bourgeron, 2015; Fetit et al., 2021). A specific genetic etiology is identifiable in up to 40% of ASD cases (Schaefer et al., 2013). It is estimated that single gene mutations account for approximately 5% of cases, and include Fragile X Syndrome, Rett Syndrome and Tuberous Sclerosis, although not all individuals diagnosed with these syndromes display autistic symptoms (Fetit et al., 2021; Jeste et al., 2016; Schaefer et al., 2013; Wulffaert, Van Berckelaer-Onnes & Scholte, 2008). In these cases, Authors speak of “syndromic autism”, to distinguish it from “non-syndromic autism”, namely idiopathic autism not associated with specific signs or symptoms (Genovese et al., 2020). Genomic Copy Number Variants (CNV), such as deletions and duplications of a given genomic section, account for another 5-10% of ASD cases (Fetit et al., 2021; Huguet et al., 2016). Most cases of ASD, however, display complex gene-gene interactions involving multiple common and rare variants (Bai et al., 2019; Genovese et al., 2020). Evidence suggests that heritability of ASD is almost exclusively due to common variants and that only a small part is attributable to rare variants. However, plentiful

common variants have been identified to date, and each seems to be associated with a low risk (Huguet et al., 2016).

Several environmental factors have been suggested to be associated with a higher risk of ASD, for instance, maternal effects such as obesity, or pregnancy complications such as maternal gestational diabetes, maternal infections during pregnancy, low birth or fetal distress; but also assisted reproductive technologies and maternal medication during pregnancy. However, with some exception (e.g., maternal valproate use, or advanced parental age), available evidence is still inconclusive (Bai et al., 2019; Modabbernia, Velthorst & Reichenberg, 2017). It is therefore more plausible that an interaction between genes-genes, and genes-environmental factors increase genetic vulnerability to ASD (Dawson, 2008; Fernandez & Scherer, 2017).

Research on the neurobiology of the ASD highlighted morphological and functional differences in the brain of autistic people. Structural magnetic resonance imaging (sMRI) studies on autistic preschool-aged children have often revealed accelerated total brain volume growth as compared to neurotypical people, which lead to increased volume of the brain, especially in the frontal and temporal lobes. Similar results have also been found in amygdala, which among other things is involved in social-emotional functioning. This subcortical brain region seems to be enlarged in autistic children (Bellani et al., 2013*b*), and studies have found a direct correlation between amygdala increased volume and severity of social and communication impairment in autistic children (e.g., Kim et al., 2010). Notably, these neuroanatomical anomalies have not been observed in autistic adolescents and adults, probably because of different gene expression abnormalities in the adolescent and adult autistic brain. Therefore, these structural differences may be age-related (Courchesne, Campbell, & Solso, 2011*b*; Ha et al., 2015). Structural abnormalities in the cerebellum of autistic children have also been observed. The most recurrent findings are hypoplasia of the vermis lobules VI-VII, as well as a reduction of Purkinje cells size in the cerebellar cortex (Courchesne, Campbell, & Solso, 2011*b;* Fatemi et al., 2002). Finally, a reduction of the corpus callosum that persist into adolescence and adulthood have been found in autistic people and has been linked to abnormal sensory processing and integration often displayed by autistic people (Bellani et al., 2013*a;* Stanfield et al., 2008).

Such anomalies have been associated with functional abnormalities and atypical connectivity frequently observed in the brain of autistic individuals. A plethora of studies have investigated neural activation of autistic people during social-related tasks, such as face processing or emotion recognition, and have found anomalies in the activation of brain regions underlying these tasks. In typically developing people, looking at human faces normally activate the fusiform gyrus (FG), situated within the ventral temporal cortex, more than when looking at non-face stimuli. In autistic individuals, instead, the activation of the FG and of other areas involved in face processing (such as

the inferior occipital gyrus and the superior temporal sulcus) is weak or absent (Pierce et al., 2021). In contrast, looking at faces may lead to the activation of other individual-specific brain regions that usually do not occur in typically developing people (TD) (*ibidem*). A meta-analysis (Aoki, Cortese & Tansella, 2015) of functional MRI (fMRI) studies on atypical emotional face processing in autistic people found supporting evidence in favor of an hyperactivation in sub-cortical regions, notably the bilateral thalamus, bilateral caudate, left cingulate and right precuneus, as well as an hypoactivation in the hypothalamus during emotional-face processing conditions, compared with TD. These regions, especially the thalamus and the caudate, make connections with specific cortical areas, creating a system for the unconscious processing of emotions, and may therefore represent the neural correlates of atypical emotion processing in ASD (Aoki, Cortese & Tansella, 2015). Notably, the Authors did not find atypical activation of cortical regions involved in emotion processing (*ibidem*).

Overall, findings presented here suggest that autistic syndrome may be attributable to deficits in cortical networks, rather than abnormalities in specific brain regions (Ha et al., 2015).

Although our understanding of the genetic and neurological mechanisms underlying ASD has improved considerably in recent years, partly thanks to the advent of new technologies, our knowledge on the matter is still limited, and therefore diagnosis remains a clinical one (Heil & Schaaf, 2013).

1.1.3 Early markers and developmental trajectories in children with ASD

ASD is a condition present from early childhood, although generally signs do not occur in the first 6 months, and core symptoms of ASD appear evident between 12 and 24 months (Zwaigenbaum, Brian & Ip, 2019). Until recently, researchers and practitioners were somewhat doubtful about the stability of an early diagnosis, since there is evidence that some children previously diagnosed with ASD lose diagnosis in late childhood or adolescence (Ozonoff et al., 2015). However, currently Authors believe that early identification of ASD is essential to promptly refer children to early interventions, given their proven efficacy in ameliorating autistic symptoms (Zwaigenbaum, Brian & Ip, 2019; Zwaigenbaum et al., 2015*c*).

First clinical manifestation of ASD can occur as early as 18 months, but more frequently around the age of two (Zwaigenbaum, Brian & Ip, 2019). Not surprisingly, given the great variability in etiology, neurobiology and clinical features characterizing ASD, behavioral signs displayed by autistic children may also vary considerably. Therefore, researchers have attempted to identify early behavioral and genetic markers to detect children at risk for ASD. Two broad categories of early markers emerge from Literature findings: reduced levels of social attention and communication, and atypical use of objects (Zwaigenbaum et al., 2015c). The formers mainly include children's lack of response when

called by name, lack of initiating and responding to joint attention, avoidance of eye contact, lack of social smile, lack of social reciprocity (Yoo, 2016; Zwaigenbaum et al., 2015c). Atypical use of objects mainly refers to repetitive behaviors, such as spinning and rotating objects, but also unusual patterns of manipulating objects and atypical sensory exploration (Yoo, 2016; Zwaigenbaum et al., 2015c). Evidence shows that most of these behaviors are evident from as early as 12 months in children later diagnosed with ASD and can discriminate them from typically developing children and even from children with other developmental delays (Zwaigenbaum et al., 2015c). Other potential early markers identified in their review, but still in need of further evidence, are atypicalities in body movements, especially repetitive stereotyped movements, and temperament profile (*ibidem*). In this regard, particularly interesting may be children characterized by lower sensitivity to social reward cues, because this is in line with the social motivation theory of ASD (Dawson, Webb & McPartland, 2005; Chevallier et al., 2012). According to this theory, social deficits such as lack of social orienting or social reciprocity displayed by autistic children, derive from an intrinsic reduced motivation towards social stimuli, accompanied by an enhanced interest for objects. Moreover, according to this framework, because of this reduced motivation, at-risk children for ASD spend less time engaging with others, missing social inputs and learning opportunities. These are crucial for the cortical specialization of the brain regions underlying social cognition, and when they are lacking, this may lead to social impairment typical of autism (Chevallier et al., 2012; Dawson, 2008). Some Authors have suggested that the reduced social motivation may be due to a deficit in understanding the reward value of social stimuli (Dawson et al., 2002). Indeed, research have shown that the reward system is compromised in autistic children, although this dysfunction seems not to be limited to social stimuli (Kohls et al., 2013).

Several Authors have also attempted to identify neurobiological markers that may help detecting children at risk for ASD. Some of them, such as abnormal brain volume or functional anomalies, have already been discussed in the previous section (see par. 1.1.2).

As already mentioned, early markers outlined above are usually evident within 12-24 months of age. Nonetheless, it may happen that parents report their child has normally acquired social and communicative functions, only to lose them between two to three years of age (Persico et al., 2020). This phenomenon is known as regression, or late-onset ASD (Bacon et al., 2018). However, lately some Authors have suggested that this regressive pattern may be more common than previously thought. For instance, Ozonoff & Iosif (2019) argue that all children at ASD onset somewhat declines in social and communication abilities, although this may happen at different ages from one child to another, and that it would be better to think of the emergence of ASD in a continuous rather than a dichotomous (early onset vs. regression) way (Ozonoff & Iosif, 2019; Pearson et al., 2018). Thus,

even in cases of regression, early signs of atypical neurodevelopment are present well before autism onset (Persico et al., 2020). Less common, nevertheless possible, is the case where acquired skills are suddenly lost after the age of 3. In this case, a thorough medical examination is essential to understand the causes of this late regression (Persico et al., 2020).

Despite professionals are stressing the importance of early detection of autistic children, in order to refer them to early interventions as soon as possible, the average age at diagnosis is still around 4-6 years (Broder-Fingert, Feinberg & Silverstein, 2018). For this purpose, efforts are being made towards early screening of children at risk for ASD. The American Academy of Pediatrics (AAP) recommends the screening for ASD of all children between 18 and 24 months, and several ASD-specific instruments have been developed in this regard (Broder-Fingert, Feinberg & Silverstein, 2018; Zwaigenbaum et al., 2015b).

ASD is a life-long condition, but clinical manifestations of autism change throughout life. Enhanced knowledge about developmental trajectories in autism is essential to ameliorate patients' care and intervention, and to date several longitudinal studies have attempted to delineate clinical trajectories and outcomes in autistic individuals (Baghdadli et al., 2012). Fountain, Winter and Bearman (2012) followed developmental trajectories of core symptoms of 6 975 autistic children from 2 to 14 years old. All children somewhat developed, although Authors report a substantial heterogeneity in developmental outcome, especially in the social domain. The biggest changes were observed in the communication domain, while restricted and repetitive behaviors (RRBs) domain remained nearly stable over time (Fountain, Winter & Bearman, 2012). This is consistent with findings from previous studies, which shows that RRBs, or at least repetitive sensorimotor and insistence on sameness behaviors displayed by autistic children remain relatively high or even worsen over time compared to children with other developmental disabilities (Richler et al., 2010). Fountain, Winter and Bearman (2012) also noticed that children classified as high-functioning at baseline were less likely to end up in low-functioning groups and vice-versa. Authors also identified a group of children, that they called "bloomers", classified as low-functioning at first referral and that improved considerably, achieving outcomes comparable to high-functioning children. No gender differences were noted, but children in the less favorable trajectory group were less likely to be white and more likely to have younger, foreign-born and less educated mothers, and to belong to low-income families (Fountain, Winter & Bearman, 2012). Interestingly, children born in more recent cohorts were more likely to have better developmental trajectories, probably because of the recent widening of diagnostic criteria to include milder cases (*ibidem*).

Pattern of growth of language abilities have also been investigated by several studies (e.g., Anderson et al., 2007; Ellis Weisner & Kover, 2015; Riva et al., 2021). Absence of expressive language, notably

first words, is usually one of the first signs reported by parents, therefore language milestones are important as prognostic indicators (Kover, Edmunds & Ellis Weisner, 2016). Although autistic children progress somewhat in language development, outcomes vary considerably from one child to another, with some children developing age-appropriate language and others who remains nonverbal or minimally verbal even in late childhood (Anderson et al., 2007; Ellis Weisner & Kover, 2015). Children whose language skills do not improve consistently are also those with more severe autistic symptoms (Anderson et al., 2007).

Children with higher severity of autistic symptoms and lower cognitive abilities are also those who improve the least in adaptive functioning (Baghdadli et al., 2012). Otherwise, there is evidence that adaptive skills ameliorate from childhood to adolescence in autistic children, despite important deficits remains. One prospective study followed more than 150 autistic children over the course of 10 years, and showed that Daily Living skills, and to some extent also social and communication abilities, improved as reported by parents (Baghdadli et al., 2012). Adaptive social abilities were found to improve into adolescence also in another research, which also showed an association between decrease is social deficits and improvement in non-verbal IQ, as well as in severity of autistic symptoms (Anderson et al., 2009).

However, research also suggest that, regardless of the ability taken into account, in autistic children the rate of improvement tends to be lower compared to children with other developmental disabilities (Anderson et al., 2007; Anderson et al., 2009). Overall, these findings suggest that although core deficits of ASD in many cases tend to remain over time, they do undergo some changes through different stages of life. Importantly, most trajectory changes occur by the age of six, and then reach a plateau (Anderson et al., 2007; Fountain, Winter & Bearman, 2012; Lord, Bishop & Anderson, 2015; Pickles et al., 2014).

1.2 Early Interventions for young children with ASD

In the previous section it was stated that ASD can be reliably detected in early childhood, generally around the age of two. Consequently, it is essential that early diagnosis is followed by early treatment. To date, there is no medical or pharmacological treatment for core symptoms of ASD. One of the main challenges in drug development for ASD is the high heterogeneity in both the etiology and the clinical manifestation of this condition, which make it difficult to identify a single pharmacological treatment that is effective in all ASD cases (Baribeau & Anagnostou, 2022). Nonetheless, psychotropic medications are often required for autistic individuals to manage challenging behaviors that interfere with behavioral treatments and more generally with social and occupational functioning (Kaplan & McCracken, 2012). Aripiprazole and risperidone, two atypical antipsychotics, are often administered in autistic people to reduce irritability and aggressive behaviors (Baribeau & Anagnostou, 2022), while selective serotonin reuptake inhibitors (SSRIs) are sometimes administered to manage highly problematic repetitive and restricted behaviors (Kaplan & McCracken, 2012).

To address social impairments, researchers have focused on oxytocin, a neuropeptide produced in the hypothalamus. This "love hormone" has proved crucial in social and emotional behaviors in several animal species, and studies have shown that oxytocin administration in healthy humans improves "mind reading" abilities, increases trust, gaze toward eyes of human faces and more generally modulates social cognition (Baumgartner et al., 2008; Domes et al., 2007; Guastella et al., 2008; Kirsch et al., 2005). Remarkably, levels of oxytocin in autistic children are lower than the norm, and therefore several Authors have attempted to administer it exogenously to enhance their social skills (Baker & Stravopoulos, 2020). However, placebo-controlled trials of oxytocin therapies in autistic children often report no significant results (e.g., Sikich et al., 2021).

Hence, interventions for ASD core symptoms fall primarily within the educational and the behavioral frameworks (Landa, 2018).

A recent review on evidence-based practices for autism identified two main types of practices: comprehensive treatment models (CTMs) and focused intervention practices (FIPs) (Wong et al., 2015). CTMs consist of a set of practices based on a well-defined theoretical framework and aim to impact broadly on the core symptoms of the autistic spectrum. Moreover, CTMs are characterized by higher intensity and longer duration than FIPs. FIPs are as well based on a clear theoretical framework, but are designed to address a specific skill or goal. Examples of FIPs are discrete trial teaching (DDT) and prompting, and are usually implemented within CTMs (Wong et al., 2015). The most frequently employed CTMs are the Early Intensive Behavioral Interventions (EIBI), the Early Start Denver Model (ESDM) (both will be fully described in the following sections), and the Treatment and Education of Autistic and Communication Handicapped Children (TEACCH)

program. This is a widely used intervention that emphasizes a close relationship between parents and practitioners and is tailored on the specific characteristics and needs of the patient, which are assessed before treatment start through standardized tests (Virués-Ortega, Julio & Pastor-Barriuso, 2013). Another CTMs often used is the Pivotal Response Treatment (PRT), a naturalistic behavioral intervention that uses play and natural reinforces to target child's social motivation and build social skills (Koegel & Koegel, 2016). All these interventions involve parents, and there are also specific versions of these interventions where the therapist is represented by the parent. Findings have shown that parent-delivered treatments are effective in improving children outcome, but also parents' satisfaction and parent-child relationship (Beaudoin, Sébir & Couture, 2019; Bibby et al., 2001; Molnár & Eldevik, 2017; Rogers et al., 2022; Siller et al., 2014; Strauss et al., 2012).

Despite the undeniable stride made in this field, there is still no standard treatment for young autistic children, especially within the public health systems. A recent survey conducted in the context of the Autism Spectrum Disorder in the European Union (ASDEU), a project aimed at collecting information from autism community to improve knowledge on the autistic condition and related costs in Europe, found that only a modest proportion (24%) of responding families reported receiving ASD-specific interventions. Families indicated that therapies to which they were referred were mainly speech-therapy or physiotherapy (Bejarano-Martín et al., 2020). However, current guidelines recommend opting for comprehensive interventions that integrate behavioral and developmental factors, as their efficacy and effectiveness have been proven in several studies (Zwaigenbaum et al., 2015). Research have shown that children treated with behavioral and developmental interventions achieve better outcomes compared to children in comparison groups receiving other kinds of treatments, especially with regard to educational placement, cognitive abilities, adaptive behaviors, language and social skills (e.g., Cohen et al., 2006; Dawson et al., 2010; Eldevik et al., 2010; Howard et al., 2005; Lovaas, 1987; McEachin, Smith & Lovaas, 1993; Rogers et al., 2019; Sallows & Graupner, 2005; Smith, Groen & Wynn, 2000; Zachor et al., 2007). It has been shown that these improvements are the result of changes in brain activity and functioning. For instance, one study found that neural response to a biological motion perception task in autistic children were more similar to those of TD children after sixteen weeks of PRT as compared to neural response registered in the same children before treatment (Ventola et al., 2015). This and similar studies show that treatments can elicit neural changes (see Calderoni et al., 2016 for a review).

This is even more true when interventions are implemented in early childhood, when brain development is remarkably sensitive to early experiences (Dawson, Ashman & Carver, 2000). Neural circuitries underpinning the "social brain" result from the early interaction between the infant and his/her social environment, with special regard to early parent-child interaction (Dawson, 2008). As

depicted in previous sections, in autistic children the genetic vulnerability and neurological anomalies in the brain regions underlying social functioning may lead to abnormal patterns of child-environment interaction, that in turn may cause anomalies in the aforementioned neural circuitries, finally leading to the clinical manifestation of the autism syndrome (Dawson, 2008). Early interventions can modify this cycle by altering the expression of risk genes and targeting processes concerning the interaction between the child and his/her partner.

The next two paragraphs illustrate the two main evidence-based approaches to EI: Applied Behavioral Analysis (ABA)-based treatment, notably the Early Intensive Behavioral Intervention (EIBI), and the Naturalistic Developmental Behavioral Interventions (NDBI). In the context of the latter, I will also introduce one of the more recent interventions that fall into the NDBI, the Early Start Denver Model (ESDM).

1.2.1 Applied Behavioral Analysis and Early Intensive Behavioral Interventions

ABA is part of the broad Behavioral Analysis (BA) and studies experimentally humans' behaviors in relation to environmental factors (Virués-Ortega, 2010). Therefore, ABA is a field of study, and its principles and procedures have been applied to a plethora of problematic behaviors, including anxiety, self-injury, aggressive and uncooperative behaviors (Peters-Scheffers et al., 2011; Roane, Fisher & Carr, 2016; Virués-Ortega, 2010).

ABA has been particularly used in the development of behavioral interventions for autism, as since the 80s research has demonstrated their effectiveness in improving autistic children's outcomes (Anderson et al., 1987; Fenske et al., 1985; Lovaas, 1987). Although EIBI treatment models differ somewhat across published studies, they all share several important features: (a) ABA-treatment is comprehensive, tailored on each child's needs, and addresses all skills domains; (b) BA procedures, such as discrete trial teaching (DTT), reinforcement, prompting, are applied; (c) treatment is intensive (usually 20-30 hours of structured sessions per week) and in most cases lasts for 2 years or more; (d) treatment is delivered by specifically trained therapists; (e) treatment is initially provided in individualized sessions and then transitions to small groups to foster socialization; (f) it is usually delivered in children's natural environment and then move on to other environments to foster generalization; (g) parents are actively involved in their children treatment (Green, Brennan & Fein, 2002).

Treatments based on ABA have become popular in this field especially after the publication of Lovaas' promising results in 1987. Ivar Lovaas, a clinical psychologist and Professor at the University of California, Los Angeles (UCLA), was the first to develop an intensive and comprehensive ABA treatment for young autistic children, also known as early intensive behavioral interventions – i.e.,

EIBI (Lovaas, 1981). In his notorious study, the Author compared 19 children pre-school aged children undergoing his manualized EIBI with two control groups, one receiving less intensive behavioral intervention (less than 10 hr per week) (Control Group 1), and one consisting of young autistic children selected from a larger sample included in a study by Freeman et al. (1985) and receiving other kind of treatments (Control Group 2). Lovaas showed that 9 (47%) children in the experimental group achieved normal cognitive and educational functioning, compared to only one out of 21 (4.8%) children in Control Group 2 and none (0%) of 19 children in the Control Group 1. Moreover, a follow-up study showed that children in the experimental group that achieved the best outcomes maintained their gains at a mean age of 11.5 years old, such that they were fully comparable to their typically developing peers on intelligence tests and adaptive behaviors (McEachin, Smith & Lovaas, 1993).

Since then, studies on EIBI have proliferated, confirming its effectiveness in improving children outcome, particularly with regard to cognitive skills, adaptive behaviors and language skills. For instance, Eikeseth and Colleagues (2002) conducted a study on 25 children, 13 treated with EIBI and 12 with eclectic treatment. Although children in both groups received on average the same amount of treatment, the Authors found that children in the EIBI group achieved larger gains on all standardized tests, especially on IQ, language skills, adaptive behaviors, and communication skills. The most marked difference was noticed in IQ, with 7 (53.8%) children in the EIBI group achieving average IQ scores, compared to 2 (16.6%) in the eclectic group. Interestingly, at intake the eclectic group scored higher than the EIBI group on almost measures (Eikeseth et al., 2002).

Cohen and Colleagues (Cohen, Amerine-Dickens & Smith, 2006) compared 21 children receiving EIBI with 21 children receiving services from public schools and found that children in the EIBI group achieved better outcome after three years of treatment. Specifically, the EIBI group increased significantly more than the control group in IQ, communication skills and daily living skills. A non-significant difference in favor of EIBI group was also found with regard to expressive and receptive language, as well as social skills. Overall, 17 of the 21 (81%) EIBI children and 1 of the 21 (4.8%) comparison children were included into regular education classes. Finally, the Authors reported that 10 (47.6%) children in the experimental group scored on the average scales on all measures (Cohen, Amerine-Dickens & Smith, 2006).

Howard and Colleagues (2005) compared the outcome and learning rate of 61 young autistic children receiving EIBI (n = 29), intensive eclectic treatment (n =16) in special education classrooms for autistic children (AP), and generic, non-intensive early intervention program for children (n = 16) with various diagnoses (GP). Results showed that, at 1-year follow-up, children in the EIBI group achieved greater mean scores in all domains, except for motor skills, compared to the two other

groups, while children in AP and GP outcome did not differ. 13 EIBI children (44.8%) obtained IQ scores in or near to the average, compared to two (12.5%) and three (18.7%) children in AP and GP, respectively. Moreover, children in the EIBI group acquired skills at a rate that corresponded to or even exceeded the normal learning rate of one year of development per year of age, while children in AP and GP learning rate was slower (Howard et al., 2005).

A more recent study also found an improvement in autistic symptoms after two years of EIBI. Smith and Colleagues (Smith, Klorman & Mruzek, 2015) evaluated the outcome of 71 autistic children receiving EIBI at 1 and 2-years follow-up. Results showed that children improved significantly in cognitive skills and adaptive behaviors, and decreased significantly in ADOS severity score, both from intake to Year 1 and from intake to Year 2. The most significant improvements occurred in the first year of treatment, except for cognitive skills (Smith, Klorman & Mruzek, 2015).

1.2.2 Naturalistic Developmental Behavioral Interventions and the Early Start Denver Model

Although effective in teaching new skills, research has shown that highly structured interventions such as EIBI may have some limitations, at least for some children, such as difficulties in generalizing learned skills or excessive dependence on prompting (Schreibman et al., 2015). These limitations have led to the design and implementation of new approaches to behavioral intervention, notably the NDBIs (*ibidem*). As EIBI, NDBIs are as well based on ABA techniques, such as reinforcement, prompting, shaping, fading and antecedent-behavior-consequence (ABC), but in addition include naturalistic and developmental components, emphasizing children's spontaneous initiatives, rather than responses to prompts (Tiede & Walton, 2019). Indeed, techniques specific to NDBIs are informed by developmental psychology, since the development and learning process of autistic children are to some extent similar to that of typically developing children (Vivanti & Zhong, 2020). Teaching in NDBIs takes place respecting the learning sequences in the acquisition of new skills, and thus the focus will be primarily on learning pivotal skills, such as joint attention, imitation and functional play, as they are the "social infrastructure" on the basis of which the learning of language, social and communication skills can occur (Vivanti & Zhong, 2020). Interventions within this framework are "naturalistic" in that learning is embedded within child daily experiences, children's behavior is reinforced by intrinsic, rather than extrinsic, rewards, and therapists and parents use an affective language naturally used with children to convey instructions, instead of concise instructions clearly defining the target behaviors (Vivanti & Zhong, 2020). In fact, learning is facilitated by affective exchange between the child and the teaching adult, and thus NDBIs aim at establishing this type of affective relationship not only as a desirable effect of treatment, but as a fundamental basis for the learning process itself (Schreibman et al., 2015; Vivanti & Zhong, 2020).

Several approaches have been developed within this framework, including the already mentioned PRT, the JASPER (Joint Attention, Symbolic Play, Engagement and Regulation) and the LEAP (Learning Experiences Alternative Program).

One type of NDBI that has received particular attention is the Early Start Denver Model (ESDM), a comprehensive early intervention specifically designed for toddlers and pre-school aged children (Rogers & Dawson, 2010b). This treatment is an expansion of the Denver Model, a developmental approach to early autism intervention developed in the 80s by Rogers and Colleagues (Rogers, Lewis & Reis, 1987). In addition to child developmental research, the ESDM draws on two important theoretical assumptions, namely the *cascade model* by Rogers and Pennington (1991) and the *social motivation theory* by Dawson and Colleagues (Dawson, Webb & McPartland, 2005). The latter has been previously discussed (see par. 1.1.3). The cascade model, instead, argues that early lack of some aspects of the interpersonal development prevents the autistic child from developing processes that lead to social engagement, such as early imitation, emotion sharing and theory of mind, and eventually interfere with the cortical specialization and behavioral expertise in the social and communication domains (Rogers & Pennington, 1991; Vivanti & Zhong, 2020).

The ESDM teaches skills across nine developmental domains, including cognition, communication skills, expressive and receptive language, imitation, joint attention, play skills, personal independence, motor skills, social skills, and treatment is provided based on the ESDM Curriculum Checklist (Rogers & Dawson, 2010a). Before treatment start, children's abilities are assessed to identify specific, short-term objectives to be learned in the next few weeks. The curriculum checklist is readministered every 12 weeks until the end of treatment in order to monitor child's progress across all developmental domain (Rogers, Vivanti & Rocha, 2017).

The efficacy and effectiveness of ESDM have now been proven by several studies in the last decade. In the first published study on ESDM outcome, Dawson and Colleagues (2010) conducted a randomized controlled trial (RCT) comparing 24 autistic preschoolers receiving an average of 15 hr per week of individualized ESDM with 21 young autistic children receiving typical community therapy (CT, also referred to "treatment as usual" in some studies). At two-years follow-up, children in ESDM group had improved significantly more than those in the control group in IQ and language skills. Moreover, while ESDM group adaptive behaviors scores remained nearly stable, the control group showed a clear decline, especially in the domain of socialization, daily living and motor skills. Children who received ESDM were also significantly more likely to have improved in symptoms severity, with 7 (29.2%) children moving from a diagnosis of autistic disorder to one of PDD-NOS, compared to 1 (4.8%) child in the control group (Dawson et al., 2010). At the end of the intervention, the Authors also collected EEG data of children from both groups and compared them with those of

typically developing peers matched by age, while looking at faces versus objects. They found that children who received ESDM showed pattern of attention engagement to social stimuli similar to those of typical children, allocating greater attention and cognitive resources during the view of faces than to the objects. On the contrary, children who received CT showed the opposite pattern (Dawson et al., 2012).

Results by Dawson et al. (2010) were partially confirmed by a recent RCT comparing ESDM and treatment as usual (TAU) outcome (Rogers et al., 2019). In this study, 55 young autistic children were enrolled in the ESDM program, and 63 in a community treatment program, in three universities. Children in the ESDM group received on average 15 hr per week of individualized treatment. After two years of intervention, the ESDM group increased significantly more than the TAU group in language composite scores (i.e., both receptive and expressive) in two out of three sites (Rogers et al., 2019).

Low-intensity ESDM also seems to be effective in improving children outcome. One study (Colombi et al., 2018) evaluated the effectiveness of 6 hr per week of ESDM for six months in a group of young children with ASD, compared to a group of autistic children receiving TAU. Children outcomes were assessed after three and six months of intervention. The ESDM group improved their overall DQ and personal-social skills significantly more than the control group after both 3 and 6 months of treatment. Children in the ESDM group made more gains in daily living, social skills and communication skills, although only the latter reached statistical significance. After 6 months of intervention, the ESDM group also increased significantly more than the TAU group in receptive and expressive language (Colombi et al., 2018).

The effectiveness of ESDM has been proven not only in 1:1 format, but also in group settings. Vivanti et al. (2014b) compared the outcome of 24 young autistic children receiving 15-25 hr per week of ESDM for 12 months in a group setting, with a child-staff ratio of 3:1, with those of 30 autistic peers receiving group community intervention, also for 12 months. Results showed that the ESDM group improved significantly more than the control group on overall DQ and receptive language. Children in the ESDM group also achieved significant gains their overall adaptive behaviors and communication skills, although not differently from the children in the control group (Vivanti et al., 2014b).

Research has also demonstrated that gains persist for years after the end of treatment. For instance, a follow-up study (Estes et al., 2015) of Dawson and Colleagues (2010) evaluated children's outcomes two years after the end of intervention and found that the ESDM group maintained the gains they made during treatment. Moreover, the Authors found that children in the ESDM group also improved

core symptoms of ASD and adaptive behaviors as compared to children in the control group, although this difference was not found immediately after the end of treatment (Estes et al., 2015).

Chapter 2.
Differential predictors of response to EIBI and ESDM in children with ASD:
a systematic review and meta-analysis

2.1 Introduction

Research has shown that autistic children treated with early and comprehensive behavioral interventions can achieve optimal outcomes. Nevertheless, studies have highlighted a great interindividual variability in rate and extent of clinical improvement, with some children showing larger gains and others only small progress (e.g., Eldevik et a., 2006; Remington et al., 2007; Sinai-Gavrilov et al., 2020; Vivanti et al., 2013). This variability is not surprising, given the great heterogeneity in etiopathogenetic underpinnings developmental trajectories, symptom patterns and severity present in the "Autisms", term used by many investigators to comprehensively refer to ASD as a heterogeneous collection of rare disorders sharing the clinical features defined as diagnostic criteria in DSM-5 (Persico et al., 2020). For this reason, researchers have attempted to identify factors that may be associated with more favorable spontaneous developmental trajectories in children at risk or initially diagnosed with ASD. The most frequently reported factors are baseline cognitive abilities and severity of autism symptoms. For example, Ellis Weismer and Kover (2015) found that ASD symptoms severity and cognitive abilities at 30 months were significant predictors of language development at 66 months, in 129 children mostly receiving behavioral interventions at the time of the final assessment. Instead, fine motor skills, and not nonverbal cognitive abilities, were positive predictors of expressive language development in two independent samples of 86 and 181 children, assessed at age 3 and again at age 19 or 10.5, respectively (Bal et al., 2020). Other factors, such as imitation and joint attention, were reported to be predictive of a favorable developmental trajectory, but not consistently in all studies. Genetic variants can also contribute to explain interindividual variability in clinical phenotype, developmental trajectories, and responsiveness to behavioral or pharmacological treatment (Cucinotta et al., 2020; Vorstman et al., 2014). Hence, heterogeneity at the pathogenetic level translates into great clinical and treatment-related interindividual differences. In addition to interindividual variability, differences in treatment methodology may also account for the different outcome observed in distinct subgroups of autistic children. This notion spurred interest in searching for predictors of a positive response to specific forms of early intensive intervention. Two studies by Schreibman and Colleagues (Schreibman et al., 2009; Sherer & Schreibman, 2005) appear to be especially interesting, as they suggest that the child characteristics associated with treatment outcome may be related to the style of treatment delivered. In their first study, Sherer and Schreibman (2005) identified two distinct behavioral profiles at baseline for responders and non-responders to PRT. The Authors assumed that children who would respond well to treatment would show more toy play, less social avoidance and more verbal self-stimulatory behaviors, and this prediction was indeed proven correct (Sherer & Schreibman, 2005). In their subsequent study

(Schreibman et al., 2009), the Authors selected six children with an incomplete "responder" profile, as three children lacked high toy play and three other children lacked low social avoidance, but in the presence of the other two predictors. These six children received PRT first, and then DTT. PRT produced no significant response in children lacking only toy play, while children lacking only social avoidance displayed intermediate improvements between those of "responders" and "non responders" in the original study (Sherer & Schreibman, 2005), pointing toward a greater role for toy play in predicting response to PRT. Importantly, the "PRT responder" profile did not predict response to DTT (Schreibman et al., 2009). These two studies, for the first time, pointed to the existence of different sets of predictors of response to different forms of behavioral treatment, lending support to the possible personalization of early intervention in newly diagnosed ASD children.

Several studies have investigated factors that may be specifically associated with positive outcomes to EIBI and ESDM, yielding variable results. Many studies reported higher intellectual functioning, measured as IQ or DQ at intake, as the strongest predictors of response to EIBI (Eikeseth et al., 2002; Eikeseth et al., 2007; Klintwall et al., 2015; Lovaas, 1987; Perry et al., 2011), although other studies have found no significant results (Cohen et al., 2006; Smith, Groen & Wynn, 2000).

Researchers and practitioners recommend starting treatment as early as possible, as this seems to positively affect intervention outcome (see Chapter 1, section 1.2). However, findings from early intervention studies have not always supported this conclusion, with only some studies finding that younger age at intake predicts better treatment outcome (Harris & Handleman, 2000; Perry et al., 2011; Robain et al., 2020; Smith et al., 2021). For instance, Lovaas (1987) did not find younger age at treatment intake to be associated with the best outcomes.

Pretreatment autism severity and language skills have also been reported to predict treatment outcome, again with mixed results (e.g., Perry et al., 2011; Magiati et al., 2007; Magiati et al., 2011 for positive results in EIBI, and Flanagan, Perry & Freeman, 2012; Harris & Handleman, 2000; Lewon & Ghezzi, 2021 for negative results in EIBI; and also Sinai-Gavrilov et al., 2020; Fulton et al., 2014 for positive results in ESDM, and Rogers et al., 2019; Rogers et al., 2021; Vivanti et al., 2014*b* for negative results in ESDM). Finally, other skills that appear to be associated with positive treatment outcome are imitation (Vivanti et al., 2013; Sallows & Graupner, 2005) and joint attention (Kasari et al., 2008; Kasari et al., 2012), but again other studies have found non-significant results (Rogers et al., 2019; Lewon & Ghezzi, 2021; Contaldo et al., 2020).

Though research have shown that both EIBI and ESDM are effective in improving children outcome, their curriculum and teaching methods are indeed different. Therefore, it is plausible that some children are more likely to respond to one treatment approach than the other, based on their underlying neurobiology and genetics, which may express a set of clinically observable pre-treatment

characteristics. Furthermore, the variable age range of children recruited in prior studies may have contributed to their discordant results, because greater deficits in a given function at an older age may reflect a more impaired underlying neurobiology, as compared to younger children, whose developmental trajectory is still at an earlier stage.

2.1.1 Predictors of outcome vs. predictors of intervention response

A conceptual distinction should be made between factors that moderate children's developmental trajectories regardless of the treatment they received vs. actual predictors of intervention response. Most of the studies published to date on predictors of outcome have a single-group pretest-posttest design or compare a specific intervention to a more general "community treatment" or "treatment as usual". Results from these studies only allow the identification of factors that contribute to a positive developmental trajectory, but not factors intervention-related that predict children's response due to that specific intervention. These can only be identified through studies with a controlled design, such as RCTs, comparing two well-specified early interventions (e.g., EIBI, ESDM, JASPER, etc.) targeting the outcome being studied (Bent et al., 2023).

2.2 Aims and Objectives

This study has two main aims: (1) to systematically review all the available literature on predictors of response to two different types of behavioral interventions, notably Early Intensive Behavioral Intervention and Early Start Denver Model, in young children diagnosed with ASD and whose treatment starts by 48 months of age; (2) to combine evidence from different studies to define first- and second-line predictors of outcome for each intervention method based on the available evidence. Focusing on studies recruiting only young children (i.e., children entering treatment before 48 months of age) should partly reduce inconsistencies and provide more helpful indications in the clinic practice. Knowing which factors are most associated with a better response to treatment in this early stage of development, and whether these factors are treatment-specific, could help clinicians prescribe the most effective intervention for each single child, at the time in life in which neuronal plasticity is at its maximum.

2.3 Methods

Studies included in this systematic review were identified through a search performed on the following databases: EmBase, PubMed, Scopus and WebOfScience (WOS) [date of search: 9 September 2022]. Our search string was as follows: (autism OR autism spectrum disorder OR asd)

AND (predictor OR predicting outcome OR outcome) AND (early intervention OR early start denver model OR esdm OR early intensive behavioral intervention OR eibi).

Study Inclusion and Exclusion Criteria and selection process

Only quantitative, empirical studies published in peer-reviewed journals were included. Studies were selected if participants were very young children under the age of four years at patient intake (i.e., 12–48 months); meeting DSM-5 criteria for Autism Spectrum Disorder, or DSM-III/DSM-IV criteria for Autistic Disorder and/or Pervasive Developmental Disorder—Not Otherwise Specified (PDD-NOS), or ICD-10 (WHO, 1993) criteria for Autistic Disorder; receiving either Early Start Denver Model or Early Intensive Behavioral Intervention applied by a certified therapist. Studies were excluded if they focused on neurodevelopmental disorders of known genetic etiology (e.g., Fragile-X Syndrome, Rett Syndrome, Tuberous Sclerosis Complex); did not report pre-treatment child characteristics as predictors of ESDM/EIBI outcome; or applied parent-mediated interventions, whereby one parent was the main therapist.

Overall, our initial search yielded 1601 articles, including 475 in WOS, 212 in PubMed, 666 in Scopus, and 248 in Embase. Articles were screened for eligibility based on title, abstract and, when appropriate, full text. We focused on children characteristics as potential predictors of treatment outcome, including anagraphical data and developmental measures, such as chronological age, cognitive abilities, language skills, and autism symptoms severity, recorded at the start of treatment. After removing duplicates from the different databases, 1121 articles were identified. 1107 studies were excluded because they did not meet our inclusion criteria (see section 2.2.1), leaving fifteen articles for this systematic review. Eight additional studies were found by searching the reference lists of relevant articles and reviews. Hence, a total of 23 articles were ultimately selected: twelve on EIBI, ten on ESDM and one on both EIBI and ESDM. The selection process is illustrated in Figure 1.

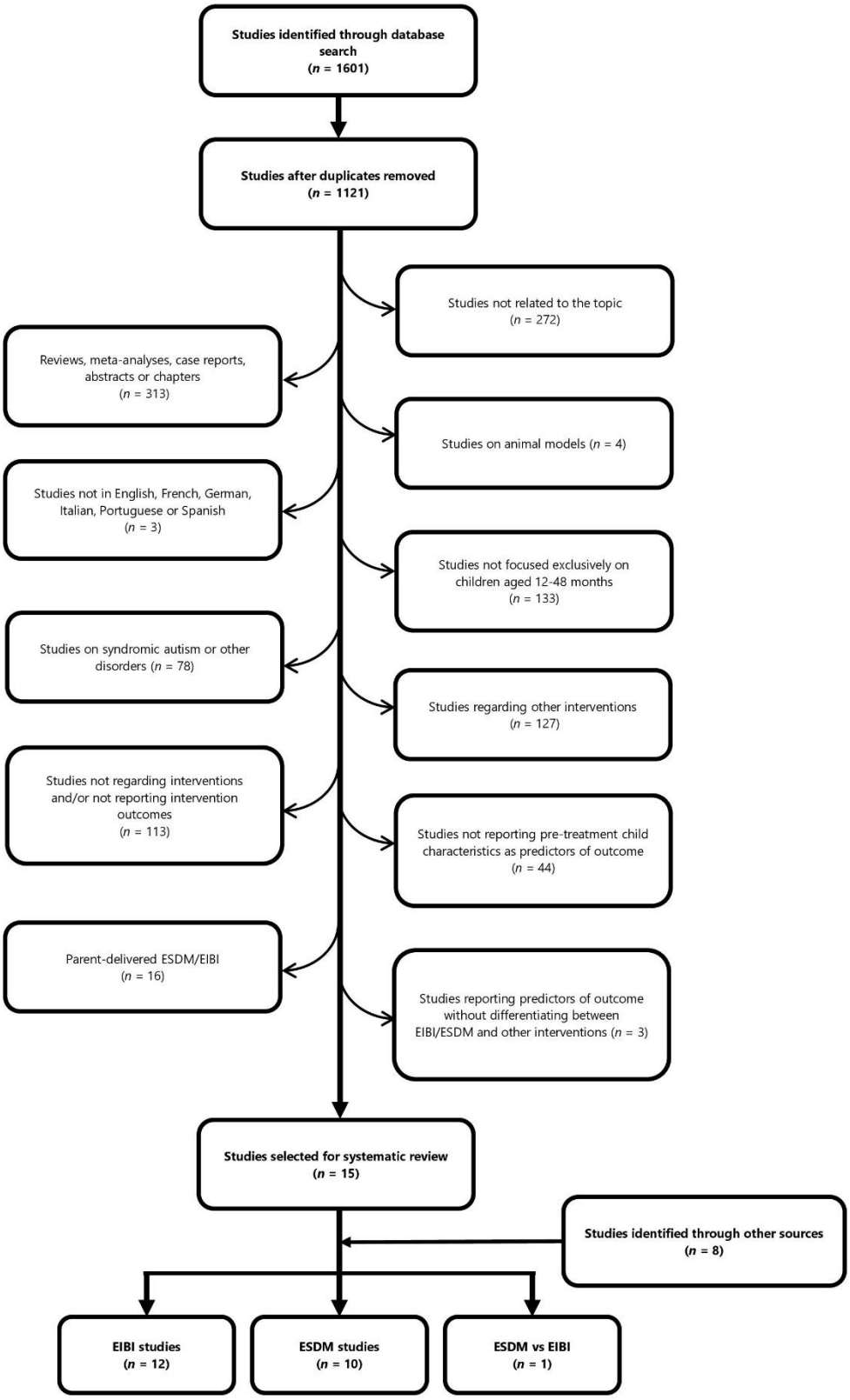


Figure 1. Study flow chart.

EIBI: Early Intensive Behavioral Intervention; ESDM: Early Start Denver Model.

2.4 Results

Overall, twenty-three articles were deemed eligible for inclusion in the systematic review: twelve on EIBI, nine on ESDM, and one on both EIBI and ESDM.

2.4.1 Early Intensive Behavioral Interventions

Thirteen publications reporting child's predictors of EIBI outcome were selected in this section. These studies include six case-control trials (Cohen et al., 2006; Lovaas, 1987; Remington et al., 2007; Sallows and Graupner, 2005; Zachor & Ben-Itzchak, 2010; Zachor et al., 2007), five single-group pre–post-treatment studies (Ben-Itzchak & Zachor, 2007; Ben-Itzchak, Watson & Zachor, 2014; Hayward et al., 2009; MacDonald et al., 2014; Sallows and Graupner, 2005), and two randomized controlled trials (RCTs) (Rogers et al., 2021; Smith, Groen & Wynn, 2000). One publication (Kovshoff, Hastings & Remington, 2011) is a two-year follow-up study of the same sample previously reported by Remington and Colleagues (2007), and therefore they will be counted and presented as a single study. Two publications (Ben-Itzchak & Zachor, 2009; Ben-Itzchak & Zachor, 2011) identified through database search were excluded because they merged the EIBI group with the comparison group in their results. These studies were on the same sample as Zachor and Ben-Itzchak (2010), which was included instead since the Authors analyzed and reported the experimental and the control groups separately. One study (Klintwall, Eldevik & Eikeseth, 2015) was excluded because it reports on the data collected from sixteen different individual publications, seven of which are included in the present review. Twenty-four articles on predictors of EIBI outcome, including three follow-up studies were excluded and will not be discussed because the age range of children at treatment start was over 48 months. However, these studies are listed for consultation in Supplementary Tables S1-S3.

Sample Characteristics

Sample characteristics are summarized in Table 1. Overall, the studies included in this section comprised 382 children with Autism Spectrum Disorder aged 12–48 months at intake, including 38 (10%) females (Remington et al., 2007; Zachor & Ben-Itzchak, 2010 and Zachor & Ben-Itzchak, 2007 did not report the gender of their experimental sample). Eight studies had a comparison group, comprising 220 autistic children aged 12–42 months, including 33 (15%) females (but Remington et al., 2007, and Zachor & Ben-Itzchak, 2010, did not report the gender of their comparison group), and 58 typically developing children aged 18–59 months (gender not reported) (MacDonald et al., 2014). In many studies, it was not possible to establish the age at which treatment actually began with any

certainty, only the age at which the child was first referred or diagnosed (e.g., Cohen, Amerine-Dickens & Smith, 2006; Remington et al., 2007).

Table 1. Summary of EIBI studies: sample characteristics.

Study	Cases				Controls			
	N (M:F)	Age at Intake in Months (Mean)	Diagnosis	Exclusion Criteria	Control Intervention	N (M:F)	Age at Intake in Months (Mean)	Diagnosis
Ben-Itzchak and Zachor, 2007	29 (25:4)	20–32 (27)	DSM-IV ADOS ADI-R	• Genetic syndromes • Seizure disorder	---	---	---	---
Ben-Itzchak et al., 2014	46 (39:7)	17–33 (25.5)	DSM-IV ADOS	• Genetic syndromes • Hearing impairment	---	---	---	---
Cohen et al., 2006	21 (18:3)	20–41 (30)	ADI-R	• IQ < 35 • Severe medical conditions	TAU	21 (17:4)	20–41 (33)	ASD
Hayward et al., 2009	23 (19:4)	24–42 (36)	ICD-10 ADI-R	• Severe medical conditions	Parent-commissioned EIBI	21 (15:6)	24–42 (34)	ASD
Lovaas, 1987	19 (16:3)	<46 (35)	DSM-III	• Age at intake > 40 mo. if non-verbal or >46 mo. if echolalic • MA ≤ 11 mo. at CA of 30 mo.	C1: low intensity EIBI C2: none	C1: 19 (11:8) C2: 21 (n.r.)	C1: <42 (41) C2: <42 (n.r.)	C1: ASD C2:ASD
MacDonald et al., 2014	83 (n.r.)	17–48 (n.r.)	DSM-IV	• n.r.	None	58 (n.r.)	18–59	TD

Study	Cases				Controls			
	N (M:F)	Age at Intake in Months (Mean)	Diagnosis	Exclusion Criteria	Control Intervention	N (M:F)	Age at Intake in Months (Mean)	Diagnosis
Remington et al., 2007 Kovshoff et al., 2011	23 (n.r.)	30–42 (36)	DSM-IV ADI-R	• Age at intake < 30 and >42 mo. • Severe medical conditions	TAU	21 (n.r.)	30–42 (38)	ASD
Rogers et al., 2021	45 (34:11)	12–30 (23)	DSM-5; ADOS-2	• Severe medical/genetic conditions • Significant vision, hearing, motor, or physical problems • DQ < 35 • Children not yet walking	ESDM	42 (32:10)	12–30 (24)	ASD
Sallows & Graupner, 2005	13 (11:2)	24–42 (35)	DSM-IV; ADI-R	• DQ < 35 • Age at intake < 24 and >42 mo. • Neurological disorders	P-EIBI	10 (8:2)	24–42 (37)	ASD
Smith, Groen & Wynn, 2000	15 (12:3)	18–42 (36)	n.r.	• Age at intake < 18 and >42 mo. • IQ < 35 and >75 • Severe medical conditions	P-EIBI	13 (11:2)	18–42 (36)	ASD

Study	Cases				Controls			
	N (M:F)	Age at Intake in Months (Mean)	Diagnosis	Exclusion Criteria	Control Intervention	N (M:F)	Age at Intake in Months (Mean)	Diagnosis
Zachor & Ben-Itzchak, 2010	45 (n.r.)	17–35 (25)	DSM-IV; ADOS; ADI-R	• Severe medical conditions	Eclectic	33 (n.r.)	15–33 (26)	ASD
Zachor et al., 2007	20 (19:1)	22–34 (28)	DSM-IV; ADOS; ADI-R	• Severe medical conditions	Eclectic	19 (18:1)	23–33 (29)	ASD

ADI-R: Autism Diagnostic Interview-Revised; ADOS: Autism Diagnostic Observation Schedule; ASD: Autism Spectrum Disorder; CA: Chronological Age; DQ: Developmental Quotient; DSM: Diagnostic and Statistical Manual of Mental Disorders; EIBI: Early Intensive Behavioral Intervention; ESDM: Early Start Denver Model; F: Females; ICD: International Classification of Diseases; IQ: Intellectual Quotient; M: Males; MA: Mental Age; n.r.: not reported; P-EIBI: Parent-Delivered Early Intensive Behavioral Intervention; TAU: Treatment as Usual; TD: Typical Development.

Participants recruited by all studies included in this review met DSM (III, IV o 5th edition) or International Classification of Diseases, 10th Revision (ICD-10; WHO, 1993) criteria for ASD, and diagnosis was confirmed by standardized instruments such as the Autism Diagnostic Observation Schedule (ADOS) or the Autism Diagnostic Instrument-Revised (ADI-R). Only one study reported that diagnosis for their participants was made by licensed psychologists independently of the study (Smith, Groen & Wynn, 2000). Authors did not include in their studies patients with severe medical conditions (Cohen, Amerine-Dickens & Smith, 2006; Hayward et al., 2009; Remington et al., 2007; Rogers et al., 2021; Smith, Groen & Wynn, 2000; Zachor & Ben-Itzchak, 2010; Zachor et al., 2007), syndromic autism (Rogers et al., 2021; Ben-Itzchak, Watson & Zachor, 2014; Ben-Itzchak & Zachor, 2007), neurological disorders (Sallows & Graupner, 2005; Ben-Itzchak & Zachor, 2007), significant hearing vision, physical or motor impairment, or children not yet walking (Ben-Itzchak, Watson & Zachor, 2014; Rogers et al., 2021). Five studies also excluded children with an IQ < 35 (Cohen, Amerine-Dickens & Smith, 2006; Rogers et al., 2021; Sallows & Graupner, 2005; Smith, Groen & Wynn, 2000) or whose mental age was ≤11 months at a chronological age (CA) of 30 months.

Treatment

Treatment characteristics are summarized in Table 2. Children in the experimental groups received individualized EIBI sessions in all studies. Autistic children in the comparison group received Eclectic Intervention (Zachor & Ben-Itzchak, 2010; Zachor et al., 2007), ESDM (Rogers et al., 2021), low-intensity EIBI (Lovaas, 1987), parent-delivered EIBI (Sallows & Graupner, 2005; Smith, Groen & Wynn, 2000), or treatment as usual (TAU) (Cohen, Amerine-Dickens & Smith, 2006; Remington et al., 2007), also defined “community therapy” in some studies. Lovaas (1987) also had a second comparison group, consisting of children studied by a different research group (Freeman et al., 1985). In one case (Hayward et al., 2009), the comparison group was composed of parent-commissioned EIBI (i.e., staff was hired and managed by parents themselves, as opposed to university-based EIBI where treatment personnel were provided by the University). Ten out of the 23 children included in Remington et al. (2007) intervention group also received parent-commissioned EIBI, but they were considered part of the EIBI group, together with children receiving clinic-delivered EIBI.

The duration of EIBI varied considerably between studies, ranging from one to four years or more. Mean treatment duration was 22 months. Intensity also varied substantially, from a minimum of 12 h/week up to 40 h/week or more. On average, children received 28 h/week. Identifying the intensity and duration of treatment received by children in the comparison groups was more difficult, as the Authors did not always clearly report this information (e.g., Remington et al., 2007; Smith, Groen &

Wynn, 2000; Zachor et al., 2007). Nevertheless, children in the comparison group received at least 19 h/week of treatment for approximately 19 months.

Baseline and outcome measures

Several abilities were taken into account as predictors of subsequent treatment response and as outcome measures. The most recurrent measures were cognitive abilities, autism symptoms severity, adaptive behaviors, language and communication abilities and social skills. In some cases, educational placement, motor skills, imitation and joint attention were also considered. Several standardized instruments were used to assess these variables across studies and even within the same research. To assess IQ, most frequently Authors administered the Bayley Scales of Infant Development (BSID; Bayley, 1993) and the Stanford–Binet Intelligence Scale (Thorndike, 1972, 1986), but also the Wechsler Preschool and Primary Scale of Intelligence–Revised (WPPSI-R; Wechsler, 1989), the Wechsler Intelligence Scale for Children—Revised (WISC-R; Wechsler, 1974), and the Mullen Scales of Early Learning (MSEL; Mullen, 1995). The Merrill–Palmer Scale of Mental Tests (Stutsman, 1948) was administered to assess visual-motor skills, while expressive and receptive skills were assessed with the Reynell Developmental Language Scales (Reynell, 1990). Adaptive behaviors were measured with the Vineland Adaptive Behavior Scales (VABS, first or second edition; Sparrow et al., 1984, 2005). Finally, as already mentioned, autism severity symptoms were evaluated with ADI-R and/or ADOS.

Table 2. Summary of EIBI studies: intervention characteristics.

Study	Country	Study Design	Intervention Type	Setting	Intensity	Duration
Ben-Itzchak & Zachor, 2007	Israel	One group pre-test–post-test	ABA	Autism-specific preschool programs	35 h/week	12 mo
Ben-Itzchak et al., 2014	Israel	One group pre-test–post-test	ABA	Centre-based	20 h/week	24 mo
Cohen et al., 2006	USA	Case–control trial	UCLA EIBI	Home-based	35–40 h/week	36 mo
Hayward et al., 2009	UK	Non-concurrent multiple baseline design	UCLA EIBI	Home-based	37 h/week	12 mo
Lovaas, 1987	USA	Case–control trial	UCLA EIBI	Home/School	>40 h/week	>24 mo
MacDonald et al., 2014	USA	Case–control trial	ABA	Home/School	20–30 h/week	12 mo
Remington et al., 2007 Kovshoff et al., 2011	UK	Case–control trial 2-year follow-up	ABA	Home-based	18–34 h/week (mean = 26)	12 mo
Rogers et al., 2021	USA	RCT	UCLA EIBI	Home/Childcare setting	12 vs. 20 h/week	12 mo

Study	Country	Study Design	Intervention Type	Setting	Intensity	Duration
Sallows & Graupner, 2005	USA	Case–control trial	UCLA EIBI	Not reported	38 h/week (gradually decreasing when children entered school)	48 mo
Smith et al., 2000	USA	RCT	UCLA EIBI	Home/Preschool	24 h/week (gradually decreasing after the first year)	24–36 mo (mean = 33)
Zachor & Ben-Itzchak, 2010	Israel	Case–control trial	ABA	Autism-specific preschool programs	20 h/week	12 mo
Zachor et al., 2007	Israel	Case–control trial	ABA	Autism-specific preschool programs	35 h/week	12 mo

ABA: Applied Behavior Analysis; EIBI: Early Intensive Behavioral Intervention; RCT: Randomized Controlled Trial; UCLA: University of California, Los Angeles.

Predictors of EIBI Treatment Outcome

Pre-treatment characteristics associated with response to EIBI are listed in Table 3. Results reported by Hayward et al. (2009) and by Sallows and Graupner (2005) refer to their entire sample, i.e., to the intervention and control group combined. However, while in Hayward and Colleagues (2009) children in control group received EIBI commissioned by parents and delivered by trained therapists, in Sallows and Graupner (2005), children received EIBI delivered directly by parents. This choice was made since Authors reported no significant differences between experimental and comparison groups in both pre- and post-treatment characteristics (*ibidem*).

Cognitive abilities

Cognitive abilities at baseline represent the most studied predictor of EIBI outcome in young children. Seven studies reported the association between pre-treatment IQ and EIBI treatment outcome, whereas four studies failed to find a correlation (Table 3). Lovaas (1987) found that children with the most favorable outcome (i.e., children who achieved normal educational and intellectual functioning) had a higher IQ and mental age at pre-intervention. In subsequent studies, children with pretreatment IQ or DQ $\geq$ 70 showed significantly greater improvements in receptive language (Ben-Itzchak & Zachor, 2007), as well as Communication, Daily living and Socialization VABS sub-domains scores (Ben-Itzchak, Watson & Zachor, 2014); performed better in ADOS scores both pre- and post-intervention (however, this result was also found in the comparison group) (Zachor et al., 2007) and had a better outcome in terms of improved IQ (Remington et al., 2007; Sallows & Graupner, 2005), possibly predicting the maintenance of improvement at two-year follow-up (Kovshoff, Hastings & Remington, 2011). In contrast to these seven positive results, four studies found no association between pre-treatment IQ and EIBI intervention outcome, although MacDonald and Colleagues reported non-significantly higher pre-treatment cognitive scores in children categorized as High/Medium Responders, as compared to Low Responders (Cohen, Amerine-Dickens & Smith, 2006; MacDonald et al., 2014; Rogers et al., 2021; Smith, Groen & Wynn, 2000). Counterintuitively, in two studies children with IQ < 70 at baseline showed a significantly greater improvement in imitation skills (Ben-Itzchak & Zachor, 2007) and in several other developmental skills, especially fine motor and receptive language (Ben-Itzchak, Watson & Zachor, 2014), compared to children with higher pretreatment IQ. Importantly, Hayward and Colleagues (2009) found that pre-treatment visuo-spatial IQ correlated not only with post-treatment visuo-spatial IQ, but also with the magnitude of improvement in global IQ, language abilities (both receptive and expressive) and adaptive behaviors at the end of EIBI.

Chronological age at intake

Four studies explored the predictive role of age at treatment onset, but only one found younger chronological age at intake to be associated with better EIBI outcome. Specifically, MacDonald and Colleagues (2014) found that children under 29 months of age were more likely to be classified as high responders and improved more than their older peers in terms of joint attention, cognitive abilities and play skills. However, the lack of a comparison group receiving another type of treatment does not allow to conclude with any certainty whether this result is specific to EIBI. In the other three studies, age at intake did not predict treatment outcome (Lovaas, 1987; Hayward et al., 2009; Remington et al., 2007).

Severity of autism symptom

Results are very mixed, as only one out of the three studies significantly support a correlation between milder autism symptoms and better outcome and/or longer maintenance of improvement after EIBI (Table 3). In fact, Zachor and Ben-Itchak (2010) report that children with milder severity symptoms (in both the EIBI and Eclectic group) showed greater gains in adaptive skills (i.e., VABS Daily Living, Communication and Socialization), cognitive and language abilities. Instead, Remington and Colleagues (2007) found that children with the best outcome showed more severe, not milder autistic symptoms, as reported by their parents. However, in their 2-year follow-up study (Kovshoff, Hastings & Remington, 2011), the Authors found that children who maintained the positive effects of EIBI displayed a non-significant ($p = 0.051$) trend toward less severe symptoms of autism, as measured by the ADI-R, upon treatment start. Finally, Rogers and Colleagues (2021) did not find any significant association between autism severity and EIBI outcome.

Language skills

In general, studies report that pretreatment language skills were primarily correlated with post-treatment language skills. A broader improvement involving additional functions was described by two out of four studies, reporting a correlation between receptive language and EIBI outcome, with a third study displaying a non-significant trend in this direction (Table 3). Smith, Groen & Wynn (2000) reported that language skills at entry were positively correlated with language skills and adaptive behaviors after two years of EIBI. Sallows and Graupner (2005) found that receptive language predicted later IQ, social and language skills. Cohen and Colleagues (2006) reported that children with the most favorable outcome (i.e., children who scored on the average range on all outcome measures) showed a trend toward a slightly better receptive language at intake, although this finding did not reach statistical significance. The same Authors did not find any significant result

regarding expressive language (*ibidem*). Finally, Rogers and Colleagues (2021) did not detect any significant association between pre-treatment language abilities and treatment outcome.

Communication skill

Two out of three studies found that more developed communication skills associated with better outcome (Table 3). Remington et al. (2007) found that children who benefited the most from treatment had higher communication skills at entry. Sallows and Graupner (2005) found that communication abilities predicted later IQ, social and language skills, together with other pre-treatment variables (Table 3). Finally, Ben-Itzchak and Zachor (2007) found no differences in the outcome of children who started treatment with higher vs. lower communication abilities, as measured by the ADOS. However, these three studies each used a different tool to assess communication skills (Table 3), and this may have contributed to their discordant results.

Social skills

Three studies assessed social skills and found them to be associated with a better outcome after EIBI treatment (Table 3). Ben-Itzchak and Zachor (2007) found that children with higher pre-treatment social skills showed greater improvement in receptive language and a trend toward slightly higher improvement in expressive language. Sallows and Graupner (2005) found that social skills predicted post-treatment IQ, language and social skills. Finally, VABS Social Skills scores were part of a panel of variables predictive of EIBI response, measured as IQ change in Remington et al. (2007). In the same sample, ADI-R social skill scores predicted persistent benefits two years after the end of treatment (Kovshoff, Hastings & Remington, 2011) (Table 3).

Adaptive behaviors

Four studies addressed adaptive behaviors, yielding mixed results (Table 3). Sallows and Graupner (2005) found that VABS Daily Living Skills was one of several variables, such as imitation, receptive language and communication skills, that best predicted post-treatment IQ, language and social skills. In another study, children with the best outcome showed better pretreatment adaptive behaviors, as measured by the VABS, but also greater problem behaviors, as measured by the Developmental Behavior Checklist (Remington et al., 2007). Adaptive behaviors were not found to predict EIBI outcome in two other studies (Cohen, Amerine-Dickens & Smith, 2006; Hayward et al., 2009).

Imitation skills

Only one study investigated and confirmed that verbal and nonverbal imitation strongly predicted post-treatment IQ, social and language skills (Sallows & Graupner, 2005) (Table 3).

Joint Attention

MacDonald and Colleagues (2014) reported that High/Medium responders to EIBI had higher tendency to initiate joint attention, but this result did not reach statistical significance.

Table 3. Predictors of better outcome after EIBI treatment.

Study	Predictors of Better Outcome	Improved Functions Correlated with Predictors	Non-Predictors
Ben-Itzchak and Zachor, 2007	• IQ—Higher • IQ—Lower • Better social skills	• Receptive language and play skills • Imitation • Receptive language (n.s. trend also for expressive language)	• Communication skills (ADOS)
Ben-Itzchak et al., 2014	• IQ—Higher • IQ—Lower	• VABS Communication, Daily living skills and Socialization scores • MSEL scores, especially Fine Motor and Receptive Language	• None reported
Cohen et al., 2006	None reported		• IQ • Language skills (n.s. trend for receptive language) • Adaptive behaviors
Hayward et al., 2009	• Higher visuo-spatial IQ	• Total IQ • Expressive and receptive language • Adaptive behaviors	• Chronological age • Adaptive behaviors • Receptive and expressive language
Lovaas, 1987	• Higher IQ/mental age	• Intellectual and educational functioning	• Chronological age

Study	Predictors of Better Outcome	Improved Functions Correlated with Predictors	Non-Predictors
MacDonald et al., 2014	• Younger chronological age	• Responding to joint attention • Initiating joint attention • Cognition • Play skills	• Cognitive abilities • Joint Attention (n.s. trend)
Remington et al., 2007	• Higher IQ/ mental age • VABS scores: higher for Adaptive behaviors, Communication, Social skills; lower for motor skills. • More behavioral problems • Greater severity of autism symptoms	• IQ	• Chronological Age • Milder severity of autism symptoms (trend)
Kovshoff et al., 2011	• ADI-R social skills	• Persistent benefits from EIBI (follow-up two years after the end of treatment)	
Rogers et al., 2021	None reported	None reported	• Autism symptom severity • MSEL DQ
Sallows and Graupner, 2005	• Imitation (verbal and nonverbal) • Higher IQ • Better receptive language • ADI-R communication • ADI-R social skills • VABS daily living skills	• IQ • Social skills • Language skills	None reported

Study	Predictors of Better Outcome	Improved Functions Correlated with Predictors	Non-Predictors
Smith, Groen & Wynn, 2000	• Language skills	• Language skills • Adaptive behavior	• IQ
Zachor and Ben-Itzchak, 2010	• Milder severity of autism symptoms	• Adaptive skills (VABS Daily living, Communication and Socialization) • Cognitive level • Language abilities	None reported
Zachor et al., 2007	• Higher IQ	• Lower ADOS scores	None reported

AD: Autistic Disorder; ADI-R: Autism Diagnostic Interview-Revised; ADOS: Autism Diagnostic Observation Schedule; IQ: Intellectual Quotient; MSEL: Mullen Scales of Early Learning; n.s.: non-significant; PDD-NOS: Pervasive Developmental Disorder Not Otherwise Specified; VABS: Vineland Adaptive Behavior Scale.

2.4.2 Early Start Denver Model

Eleven studies on ESDM reporting predictors of outcome were selected. Four articles focused on one-group pre–post-test studies (Contaldo et al., 2019; Godel et al., 2022; Sulek et al., 2022; Zitter et al., 2021) and one was an observational retrospective study (Devescovi et al., 2016). Three studies were randomized controlled trials (RCTs) (Rogers et al., 2019; Rogers et al., 2021; Vivanti et al., 2019). Three studies were case–control trials (Latrèche et al., 2021; Vivanti et al., 2016; Wang et al., 2022). Latrèche and Colleagues (2021) conducted both a cross-sectional and a longitudinal analysis, comparing autistic children with typically developing children and autistic children receiving ESDM vs. TAU, respectively. Eight additional studies were not included, since some children were older than 48 months at treatment start, but the sample characteristics, intervention strategies and outcome of these studies are summarized for consultation in Supplementary Tables S4–S6.

Sample Characteristics

Overall, these eleven studies investigated predictors of ESDM outcome in 468 children, including 107 (22.8%) females, aged 12–48 months at intake based on our study-selection criteria. A summary of sample characteristics can be found in Table 4. Four studies (Latrèche et al., 2021; Rogers et al., 2019; Rogers et al., 2021; Wang et al., 2022) had a control group, consisting of 206 autistic children, including 41 (19.9%) females, aged 12–48 months at intake. Latrèche and Colleagues (2021) also included a second comparison group consisting of 16 typically developing children (females n = 4, 25.0%). One study (Vivanti et al., 2016) compared outcomes of younger children (18–48 months) with 28 older autistic children aged 48–62 months at intake, both receiving ESDM.

Participants included in these studies all met DSM-IV or DSM-5 criteria for ASD, and the diagnosis was confirmed by ADOS or ADOS-2. Children were excluded if they had severe medical conditions other than ASD (Godel et al., 2022; Rogers et al., 2019; Rogers et al., 2021; Vivanti et al., 2016; Wang et al., 2022), neurological disorders (Contaldo et al., 2020; Godel et al., 2022; Devescovi et al., 2016; Wang et al., 2022), genetic syndromes (Contaldo et al., 2020; Godel et al., 2022; Devescovi et al., 2016) and significant vision, hearing, motor or physical impairment (Contaldo et al., 2020; Devescovi et al., 2016; Rogers et al., 2019; Rogers et al., 2021; Vivanti et al., 2016; Wang et al., 2022). Two studies excluded children with a Developmental Quotient (DQ) > 35; children born at a gestational age of less than 34 months, and children not yet walking (Rogers et al., 2019; Rogers et al., 2021). Finally, one study reported no exclusion criteria based on child behaviors or cognitive abilities (Vivanti et al., 2019), and three others did not specify exclusion/inclusion criteria (Latrèche et al., 2021; Sulek et al., 2022; Zitter et al., 2021).

Table 4. Summary of ESDM studies: sample characteristics.

Study	Cases				Controls			
	N (M:F)	Age at Intake in Months (Mean)	Diagnosis	Exclusion Criteria	Control Intervention	N (M:F)	Age at Intake in Months (Mean)	Diagnosis
Contaldo et al., 2019	32 (26:6)	18–39 (29)	ADOS-2	• Genetic syndromes • Neurological disorders • Significant vision, hearing, motor, or physical impairment	---	---	---	---
Devescovi et al., 2016	21 (18:3)	20–36 (27)	DSM-5 ADOS-2	• Genetic syndromes • Neurological disorders • Significant vision, hearing, motor, or physical impairment	---	---	---	---
Godel et al., 2022	55 (48:7)	15–42 (29)	DSM-5 ADOS-2	• Severe somatic, neurologic or genetic condition that could have affected the validity of behavioral measures (e.g., cerebral palsy, epilepsy, etc.)	---	---	---	---
Latrèche et al., 2021	51 (45:6)	17–48 (34)	ADOS-2	• n.r.	**C1** = CT **C2** = None	**C1**: 30 (25:5) **C2**: 16 (12:4)	**C1**: 17–48 (34) **C2**: 17–48 (30)	**C1**: ASD **C2**: None
Rogers et al., 2019	55 (41:14)	14–29 (21)	DSM-IV ADOS-2	• Severe medical/genetic conditions • DQ < 35 • Gestational age < 35 wks • Children not yet walking	CT	63 (51:12)	14–29 (21)	ASD

Study	Cases				Controls			
	N (M:F)	Age at Intake in Months (Mean)	Diagnosis	Exclusion Criteria	Control Intervention	N (M:F)	Age at Intake in Months (Mean)	Diagnosis
Rogers et al., 2021	42 (32:10)	12–30 (24)	DSM-5 ADOS-2	• Severe medical/genetic conditions • DQ < 35 • Significant vision, hearing, motor, or physical impairment • Children not yet walking	EIBI	45 (34:11)	12–30 (23)	ASD
Sulek et al., 2022	99 (70:29)	14–47 (32)	ADOS-2	• n.r.	---	---	---	---
Vivanti et al., 2016	32 (26:6)	18–48 (33)	DSM-5 ADOS	• Severe medical/genetic conditions • Significant vision, hearing, motor, or physical impairment	ESDM	28 (25:3)	48–62 (49.5)	ASD
Vivanti et al., 2019	44 (27:17)	15–32 (26)	DSM-5 ADOS-2	• No exclusion criteria based on child behavior or cognition	---	---	---	---
Wang et al., 2022	21 (17:4)	18–36 (21)	DSM-5 ADOS	• Neurodevelopmental disorders of known genetic etiology • Developmental disorder other than ASD • Cerebral palsy • Hearing disorder	None (Waitlist for ESDM)	24 (18:6)	18–36 (22)	ASD
Zitter et al., 2021	16 (11:5)	20–39 (29)	ADOS-2	• n.r.	---	---	---	---

ADOS: Autism Diagnostic Observation Schedule; ASD: Autism Spectrum Disorder; CT: Community Therapy; DQ: Developmental Quotient; DSM: Diagnostic and Statistical Manual of Mental Disorders; EIBI: Early Intensive Behavioral Intervention; ESDM: Early Start Denver Model; n.r.: not reported.

Treatment

ESDM treatment characteristics are summarized in Table 5. Seven studies delivered individualized ESDM sessions (Devescovi et al., 2016; Godel et al., 2022; Latrèche et al., 2021; Rogers et al., 2019; Rogers et al., 2021; Wang et al., 2022; Zitter et al., 2021), three delivered group-setting ESDM (Sulek et al., 2022; Vivanti et al., 2016; Vivanti et al., 2019), while Contaldo and Colleagues (2020) provided a mix of individualized and group ESDM sessions. Children received, on average, 13 h/week of ESDM (range: 3–20) for an overall mean duration of 15 months (range: 10–24). Children in comparison groups received CT (Rogers et al., 2019; Latrèche et al., 2021), or EIBI (Rogers et al., 2021), for an average of 14 h/week (range: 3.4–20) for approximately 18 months (range 12–24). Vivanti et al. (2016) provided ESDM to children in the older group with the same intensity (20 h/week) and for the same duration (12 months) as children in the younger group. Finally, children in the Wang and Colleagues (2022) comparison group were on a waiting list to ESDM.

Predictors of ESDM Treatment Outcome

Pre-treatment characteristics associated with response to ESDM are listed in Table 6.

Cognitive abilities

Five out of seven studies found an association between cognitive abilities and several outcome measures. Contaldo and Colleagues (2020) found that a higher developmental age at entry was associated with faster gains in "Socialization", and "Cognition and Play" ESDM-checklist domains, as well as the rate of learning (operationalized as the number of objects acquired in one months by each child). Rogers and Colleagues (2019) found that children with a higher DQ at baseline had lower autistic scores on the ADOS at the end of treatment. Two studies found that DQ at baseline predicted DQ at the end of treatment (Godel et al., 2022; Sulek et al., 2022). Surprisingly, Devescovi et al. (2016) found that children with a DQ below 75 at baseline showed greater post-treatment improvement in cognitive and language scores compared to their peers, whose DQ was ≥75. Finally, two studies did not find any association between cognitive abilities and any outcome measure (Rogers et al., 2021; Zitter et al., 2021).

Table 5. Summary of ESDM studies: intervention characteristics.

Study	Country	Study Design	Setting	Intensity	Duration
Contaldo et al., 2019	Italy	One group pretest-posttest	Community-based (GS)	4 h/week (2 h GS; 2 h 1:1)	8–16 mo (mean 12 mo)
Devescovi et al., 2016	Italy	Retrospective study	Community-based	3 h/week	11–19 mo (mean 15 mo)
Godel et al., 2022	Switzerland	One group pretest-posttest	Center-based	20 h/week	24 mo
Latrèche et al., 2021	Switzerland	Case–control trial	n.r.	20 h/week	24 mo
Rogers et al., 2019	USA	RCT	Home/Preschool/Daycare	20 h/week	24 mo
Rogers et al., 2021	USA	RCT	Home/Daycare	12 vs. 20 h/week	12 mo
Sulek et al., 2022	Australia	One group pretest-posttest	Childcare setting (GS)	~15 h/week	12 mo
Vivanti et al., 2016	Australia	Case–control trial	University-based (GS)	15–25 h/week	12 mo
Vivanti et al., 2019	Australia	RCT	School-based (GS)	15 h/week	10 mo
Wang et al., 2022	China	Case–control trial	Hospital-based	1 h/week	6 mo
Zitter et al., 2021	USA	One group pretest-posttest	Clinic-based	4 h/week	12 mo

DQ: Developmental Quotient; GS: Group-setting ESDM; RCT: Randomized Controlled Trial.

Table 6. Predictors of positive outcome after ESDM treatment.

Study	Predictors of Better Outcome	Improved Functions Correlated with Predictors	Non-Predictors
Contaldo et al., 2019	• Receptive language • Higher DQ • Lower autism symptoms severity • First communicative gestures repertoire • Action with objects	• Socialization, cognition, play and motor ESDM-checklist domains • Rate of learning • Communication ESDM-checklist domain	• Age at intake • Imitation • Word production
Devescovi et al., 2016	• Younger age at intake • Lower DQ (<75)	• Greater improvement in severity of autism symptoms • Greater improvement in cognitive and language scores	• None reported

Study	Predictors of Better Outcome	Improved Functions Correlated with Predictors	Non-Predictors
Godel et al., 2022	• Higher MSEL DQ • Higher VABS-II Adaptive Behavior Composite and Communication score • Higher Expressive and Receptive Language MSEL • Higher Visual Reception MSEL • Higher Fine Motricity MSEL • Lower stereotyped and repetitive behaviors (ADOS RRB) • Early developmental progress (i.e., rate of change) by 6 months of intervention	• Rate of DQ change	• Symptom severity (ADOS CSS)
Latrèche et al., 2021	• Attention to faces	• MSEL DQ • Verbal DQ	• None reported
Rogers et al., 2019	• Higher DQ at baseline	• Lower ADOS scores	• Joint Attention • Severity of autism symptoms • Play skills • Expressive and receptive language skills
Rogers et al., 2021	None found		• Severity of autism symptoms • MSEL DQ

Study	Predictors of Better Outcome	Improved Functions Correlated with Predictors	Non-Predictors
Sulek et al., 2022	• MSEL DQ • Speech-related vocalization ratio*	• MSEL DQ	None reported
Vivanti et al., 2016	• Younger age at intake • Initial language	• Verbal DQ	None reported
Vivanti et al., 2019	• Younger age at intake	• Verbal DQ	None reported
Wang et al., 2022	• Less stereotyped and repetitive behaviors (ADOS RRB)	• Improvement in cognitive verbal/preverbal	• Severity symptoms (ADOS Communication and ADOS Social) • Age at independent walking
Zitter et al., 2021	• Older age at intake	• Learning response rate	• Severity of autism symptoms • Stereotyped and repetitive behaviors • Adaptive behaviors • MSEL DQ

*Speech-related sounds/non-speech sounds. DQ: Developmental Quotient; IQ: Intellectual Quotient; MSEL: Mullen Scales of Early Learning.

Chronological age at intake

Five studies addressed the possible association between age at treatment onset and final outcome. Pre-treatment chronological age was found to predict ESDM outcome in four of these five studies. Devescovi and Colleagues (2016) found that entering ESDM before 27 months predicted greater improvements in autistic symptoms severity. Vivanti and Colleagues (2016) compared younger children (18–48 months) with older children (48–62 months) receiving ESDM and found that younger children reached significantly larger gains on verbal DQ after one year of treatment, and that this result was moderated by initial language skills. Similarly, the same group also found that a younger age predicted verbal DQ, regardless of other factors (Vivanti et al., 2019). Counterintuitively, Zitter et al. (2021) found that age at intake was positively correlated with child-learning response; that is, older children responded more quickly to ESDM. Finally, no association between chronological age and any outcome measure was reported by Contaldo and Colleagues (2020).

Severity of autism symptoms

Six studies investigated the possible association between ASD symptom severity and treatment outcome (Contaldo et al., 2020; Godel et al., 2022; Rogers et al., 2019; Rogers et al., 2021; Wang et al., 2022), and all but one yielded negative result. In the only positive study, milder autism severity predicted greater gains in Socialization, Cognition, Play, and Motor ESDM-checklist do-mains, as well as in the rate of learning (i.e., number of learning objectives acquired by each child in one month) (Contaldo et al., 2020).

Language skills

Three out of four studies support receptive language and non-verbal communication as predictive of outcome after ESDM. Sulek and Colleagues (2022) found that children vocalization ratio (i.e., a measure of speech-related sounds compared to non-speech sounds, such as vegetative sounds) was predictive of post-treatment DQ, together with pre-treatment DQ. Similarly, Godel and Colleagues (2022) found that expressive and receptive language skills predicted DQ and rate of DQ change at the end of treatment. Contaldo and Colleagues (2020) found that receptive language, but not word production, was significantly associated with gains in Socialization, Cognition and Play, and Motor ESDM-checklist domains, as well as with the rate of learning. Non-verbal communication, notably first communicative gestures repertoire and action with objects, were also associated with greater gains in the Communication ESDM-checklist domain (Contaldo et al., 2020). Instead, Rogers and Colleagues (2019) found that language abilities did not influence the effect of ESDM.

Attention to face

One study reported that higher levels of attention to faces, operationalized as the percentage of time spent staring at a face measured through an eye-tracking task, is predictive of children showing higher gains in overall DQ and verbal DQ after ESDM (Latrèche et al., 2021).

Stereotyped and repetitive behaviors

Three studies investigated whether this factor was associated with ESDM response. One of these reported no significant results (Zitter et al., 2021), while the other two found that lower repetitive behaviors at baseline predicted improvement in overall DQ (Godel et al., 2022) and cognitive verbal/preverbal (Wang et al., 2022) post-treatment.

Imitation, joint attention, play skills, and adaptive skills.

Imitation, joint attention and play skills did not possess significant predictive power on ESDM outcome in single studies involving young children (Contaldo et al., 2020; Rogers et al., 2021). Better adaptive skills were found to predict improvement in post-treatment DQ in only one study (Godel et al., 2022), while another was negative (Zitter et al., 2021).

2.5 Meta-analysis and summary of results

To quantitatively systematize the literature data, p-values from different studies assessing the same putative predictor were combined using Fisher's method (Fisher, 1932). This statistic was chosen because the association between each putative predictor and treatment outcome was tested using different statistical methods across multiple studies (t-tests, ANOVAs, Pearson's correlation, regression analysis). Briefly, Fisher's method combines p-values from *k* independent tests of the same null hypothesis (H0), into one chi-squared ($\chi 2$) statistics with 2k degrees of freedom, providing a single combined p-value (Fisher, 1932), as follows:

$$X_{2k}^2 \sim -2\sum_{i=1}^{k}\log(p_i),$$

To perform this meta-analytic procedure, p-values were recorded or extrapolated from each study. When more than one association between a putative predictor and an outcome variable was reported in the same study, the smallest p-value was chosen. When not explicitly reported, p-values were calculated from the available test statistics using GraphPad QuickCalcs Website [https://www.graphpad.com/quickcalcs/pvalue1.cfm (accessed on October 4, 2022)]. Fisher's method was performed in R version 4.1.2 (R Core Team, 2021), using the "fisher" function of the "poolr" package (Cinar & Viechtbauer, 2022). Results are summarized in Table 7.

Table 7. Predictors of better response to EIBI and to ESDM, categorized based on number of published articles, percentage of positive studies, and combined *p*-value obtained using the Fisher's method.

	EIBI			ESDM		
	Variable	**N. (%) of Positive Studies**	**Fisher's Statistics ***	**Variable**	**N. (%) of Positive Studies**	**Fisher's Statistics ***
First-line predictors	Higher IQ/DQ at intake	7/11 (63.6%)	$\chi^2 = 83.968$, $df = 20$ $p = 8.24 \times 10^{-10}$	Verbal and non-verbal intention to communicate; attention to faces	5/6 (83.3%)	$\chi^2 = 77.733$; $df = 12$; $p = 1.12 \times 10^{-11}$
Second-line predictors	Better receptive language abilities	2/4 (50%)	$\chi^2 = 38.399$; $df = 8$; $p = 6.35 \times 10^{-10}$	Higher IQ or DQ at intake, action with objects	5/7 (71.4%)	$\chi^2 = 61.444$; $df = 14$; $p = 6.54 \times 10^{-8}$
	Greater social skills	3/3 (100%)	$\chi^2 = 23.799$; $df = 6$; $p = 5.69 \times 10^{-4}$	Younger age at intake	3/5 (60%)	$\chi^2 = 25.633$; $df = 8$ $p = 0.0012$
	Communication skills	2/3 (66.6%)	$\chi^2 = 17.710$; $df = 6$; $p = 0.007$	Less stereotyped and repetitive behaviors	2/3 (66.7%)	$\chi^2 = 14.854$; $df = 6$ $p = 0.021$
Weak or non-predictors	Adaptive behaviors	2/4 (50%)	$\chi^2 = 18.757$; $df = 6$; $p = 0.0046$	Milder severity of autistic symptoms	1/6 (16%)	$\chi^2 = 22.565$; $df = 12$ $p = 0.032$
	Younger age at intake	1/4 (25%)	$\chi^2 = 24.048$; $df = 4$; $p = 7.81 \times 10^{-5}$			
	Milder severity of autistic symptoms	1/3 (33.3%)	$\chi^2 = 20.802$; $df = 6$ $p = 0.002$			

	EIBI			ESDM		
	Variable	N. (%) of Positive Studies	Fisher's Statistics *	Variable	N. (%) of Positive Studies	Fisher's Statistics *
Insufficient evidence	Imitation	1/1	---	Adaptive behaviors	1/2	---
	Joint Attention	0/1	---	Imitation	0/1	---
				Joint attention	0/1	---
				Play skills	0/1	---

*Degrees of freedom (df) are reported in round brackets. If df < 2N, no statistics could be retrieved from one or more original article.

First, we considered the number of studies addressing each pre-treatment variable in connection with post-treatment outcome. We then quantified the amount of available evidence in favor of each putative predictor, in terms of number of studies reporting a positive association between predictor and outcome, as well as cumulative p-value for each obtained predictor, combining all published statistical outcomes from multiple studies using Fisher's method.

First-line predictors are supported by more than 50% of the available studies for each treatment approach, with a cumulative p-values in the range of $10^{-10}/10^{-11}$. Second-line predictors appear promising, as they also are supported by at least 50% of the available studies, but have been assessed in fewer articles and/or yield a cumulative p-value below the above-mentioned range. Other pre-treatment variables appear, at this stage, to be "Weak or non-predictors", because they have been found to be associated with outcome in a minority of studies and/or with cumulative p-values $< 10^{-5}$. Finally, special caution is required with variables assessed only in one or two studies, as insufficient evidence is currently available (Table 7).

Applying this stratification framework to studies regarding EIBI, we found that the most studied and reliable factor associated with outcome in young autistic children is IQ/DQ at intake, since seven out of eleven studies support its predictive power, reaching an impressive combined p-value (section 2.4, Table 7). Interestingly, visuo-spatial IQ can especially be developed in EIBI positive responders (Hayward et al., 2009). Promising second-line predictors of better outcome after EIBI were also identified, although more studies are required to conclusively confirm and quantify their predictive power. These include better receptive language abilities, communication skills, and social skills. Variables unlikely to be associated with EIBI outcome surprisingly include younger age at intake and milder severity of autistic symptoms. Adaptive behaviors also yield very mixed results, which may reflect that this is a complex construct engaging multiple underlying skills. Imitation and joint attention have each been the object of a single EIBI study to date (Sallows & Graupner, 2005), therefore no conclusions can be drawn at this time.

For ESDM, the broader construct of pretreatment "social cognition" appears to predict a positive response in five out of six studies assessing communication (verbal and non-verbal) and attention to faces (Table 7). In particular, verbal (receptive and expressive language) and non-verbal (gestures) communication skills were collectively assessed in five studies, one negative (Rogers et al., 2019) and four documenting greater improvements associated with better language skills at intake (Contaldo et al., 2020; Vivanti et al., 2016), higher expressive and receptive language (Godel et al., 2022), a broader repertoire of first communicative gestures (Contaldo et al., 2022), and greater intentional communication in the form of more speech-related vs. non-speech related vocalizations (Sulek et al., 2022), albeit not necessarily full word production (Contaldo et al., 2020). Meanwhile, another key

feature in social cognition, i.e., attention to faces assessed by eye-tracking, was also predictive of better response to ESDM in one study (Latrèche et al., 2021). Promising, but more mixed results, pre-treatment IQ/DQ, chronological age at intake, and stereotyped/repetitive behaviors. Five studies investigated the predictive role of age at intake: three found that younger children made the biggest progress (Devescovi et al., 2016; Vivanti et al., 2016; Vivanti et al., 2019), one study found that older children achieved greater improvements (Zitter et al., 2021), while one study was negative (Contaldo et al., 2020) (Table 6). Six studies investigated the predictive power of DQ at the beginning of treatment over response to ESDM, with four studies finding an association between greater post-treatment response and higher pre-treatment DQ (Contaldo et al., 2020; Godel et al., 2022; Rogers et al., 2019; Sulek et al., 2022), one study finding lower DQ predictive of greater post-treatment gains (Devescovi et al., 2016), and two studies reporting no association (Rogers et al., 2021; Zitter et al., 2021). Interestingly, most studies tend to exclude a predictive role for the severity of autism symptoms prior to ESDM, which, despite being addressed by six studies, only reaches a cumulative p-value of 0.032 (Table 7). More research is needed, especially research focused on younger children, to draw firm conclusions on adaptive behaviors, imitation, joint attention, and play skills, each mostly not supported by single studies (Table 6), but with some positive results in research involving older children (see Supplementary Table 6).

Chapter 3.
Behavioral and developmental predictors of response to the Early Start Denver Model: a nine-month longitudinal study in 32 young children with ASD

3.1 Introduction and purpose of the study

In recent years, research has increasingly highlighted the heterogeneity characterizing the ASD, both in the clinical manifestations of the disorder and from a genetic point of view, and also in the different neurocognitive mechanisms that appear to underly ASD (Vivanti et al., 2014a; Persico et al., 2020). Not surprisingly, this heterogeneity is reflected in treatment outcome, with some children achieving remarkably results and others only small progress (e.g., Cohen, Amerine-Dickens & Smith, 2006; Fulton et al., 2014; Lovaas, 1987; Vivanti et al., 2013).

A growing body of research has attempted to identify children's behavioral and developmental factors associated with a positive response to early interventions. Knowledge on this topic is essential to help families and practitioners identify the most effective treatment for their children (Vivanti et al., 2014a).

In the systematic review and meta-analysis depicted in the previous chapter, we aimed at gathering and reviewing evidence produced to date on children's behavioral and developmental predictors of positive response to two of the most efficacious early interventions, notably EIBI and ESDM. Although not definitively, our findings allowed us to identify specific pre-treatment variables that may help predict children outcome. Moreover, it appears that at least some of these factors are preferential predictors of a specific kind of treatment.

In the present chapter, I will introduce an experimental longitudinal study on behavioral and developmental predictors of response. The study was conducted on a sample of 32 young autistic children entering treatment before 48 months of age, receiving individualized ESDM sessions for nine months.

Several studies have now proven the efficacy and effectiveness of the ESDM in several contexts, including in Italy (e.g., Colombi et al., 2018). We expected that, at a group level, children in our sample would benefit from ESDM, especially on the language, socio-communication, and cognitive domains. However, we also expected to find great variability in treatment outcome at an individual level. Therefore, the purpose of this study was twofold: 1) to quantify the rate of Full Responders (FR), Partial Responders (PR) and Low Responders (LR) to ESDM; 2), to characterize FR, PR and LR on a clinical and psychodiagnostics level.

Informed by findings reported in Chapter 2, our main hypothesis was that children outcome would be primarily predicted by pre-treatment socio-communication and language skills. Moreover, based on the ESDM theoretical framework, we hypothesized that children with less impaired eye contact,

joint attention, imitation and play skills at intake would be more likely to show a positive response to ESDM.

3.2 Materials and Methods

3.2.1 Participants

Participants included in our sample were 26 (81.25%) boys and 6 (18.75%) girls aged 20-39 months (mean 29.66, see Table 8) referred for early intervention to the University Hospital "G. Martino" of Messina, Italy.

Inclusion criteria were chronological age between 20 and 48 months at treatment start, and meeting DSM-5 diagnostic criteria for ASD. Children were excluded if they were diagnosed with a neurodevelopmental disorder of known genetic etiology (e.g., Fragile X Syndrome), if they suffer from a neurological disorder (e.g., epilepsy), if they displayed a brain malformation, or if they received a diagnosis of Global Developmental Delay (GDD).

Main participants pre-treatment characteristics are summarized in Table 8.

Table 8. Pre-treatment characteristics of participants.

	N	Mean (SD)	Range
Chronological age	32	29.66 (4.48)	20-39
Gender (M:F)	32	26:6	---
ADOS-2 Total	24	17.83 (4.78)	9-30
GMDS-ER GQ	32	60.8 (17.72)	21-100
VABS CS	25	66.33 (12.07)	42-88

ADOS: Autism Diagnostic Observation Schedule; F: Females; CS: Composite Score; GMDS-ER: Griffith Mental Developmental Scale – Extended Revised; GQ: Global Quotient; M: Males; VABS: Vineland Adaptive Behavior Scale.

3.2.2 Procedures

A comprehensive assessment of children autism severity, cognitive, language and other behavioral data was carried out at the beginning of the study. Measures were collected right before the start of the ESDM (T0) and at the end of treatment (T2). A mid-term evaluation (T1) was carried out four months after treatment start to monitor each child's progress, with the sole administration of PEP-3 and VAS scales. A brief outline of the tests administered during the different phases of the study is shown in Figure 2.

Figure 2. Instruments administered for the assessment at T0, T1 and T2.

ABC: Aberrant Behavior Checklist; ADI-R: Autism Diagnostic Interview-Revised; ADOS: Autism Diagnostic Observation Schedule; CBCL: Child Behavior Check List; CGI: Clinical Global Impression Scale; GMDS-ER: Griffith Mental Developmental Scales-Extended Revised; Q-Chat: Quantitative-Checklist for Autism in Toddlers; QOL-A: Quality of Life in Autism Questionnaire; PEP: Psychoeducational Profile; RBS-R: Repetitive Behavior Scale-Revised; SRS: Social Responsiveness Scale; SSP: Short Sensory Profile; VABS: Vineland Adaptive Behavior Scale; VAS: Visual Analogue Scale; WHQoL: World Health Organization Quality of Life Assessment.

Based on the assessment of children's skills conducted before treatment start, for each child an individualized ESDM plan was developed. Children received 6hr per week of individualized ESDM session for a duration of nine months. Each session lasted 90 min each and was delivered four times a week by ESDM-certified therapists at the Interdepartmental Program "Autism 0-90".
The study protocol was approved by the local ethical committee.

3.2.3 Measures

ADOS-2 (Lord et al., 2012) was administered to confirm ASD diagnosis and to assess the severity of symptoms. This instrument comprises two scales, the Social Affect (SA) and the Repetitive and Restricted Behaviors (RRB); in addition, it provides a total severity score. The ADOS-2 consists of 5 modules, and the appropriate one to be administered is identified on the basis of the child's expressive language and chronological age. At intake, twenty children in our sample were administered the Toddler Module, three the Module 1, and one child received the Module 2. The remaining 8 children lacked ADOS-2 at intake.
Autism severity symptoms were also assessed through the ADI-R (Lord, Rutter & Le Couteur, 1994), a semi-structured interview administered to caregivers usually used together with ADOS-2. ADI-R provides information on three domains, namely social interaction (A), communication (B) and restricted, repetitive, and stereotyped patterns of behavior (C), as well as on anomalies in the development before 36 months (D). The first three scales each have 3 subscales investigating specific aspects of those domains.
Children were also categorized as "requiring support" (Level 1), "requiring substantial support" (Level 2) and "requiring very substantial support" (Level 3), according to their symptoms severity level as delineated in DSM-5 (APA, 2013).
Participants' cognitive level was assessed through the Griffith Mental Developmental Scales-Extended Revised (GMDS-ER; Griffiths, 1984), a standardized developmental assessment for children up to seven years old. This instrument comprises six subscales: Locomotor, Personal-Social, Language, Eye and Hand Co-ordination, Performance, and Practical Reasoning. This last one is intended for children aged two to eight years, and therefore was administered only to two of the children included in our sample and will not be taken into account in our statistical analysis. For each subscale of the GMDS-ER, the relative mental age can be calculated, as well as a global development quotient (DQ).
Children's developmental profile was also assessed through the Psychoeducational Profile-Third Edition (PEP-3; Schopler et al., 2005), a scale designed to measure skills and behaviors of children with autism and communication disabilities. Domains assessed by PEP-3 include Visual-Motor

Imitation (VMI), Cognitive Verbal/Preverbal (CVP), Expressive Language (EL), Receptive Language (RL), Fine Motor (FM) and Gross Motor (GM).

The Vineland Adaptive Behavior Scale – Second Edition (VABS-II; Sparrow, Cicchetti & Bella, 2005), a semi-structured caregiver interview, was administered to assess children's adaptive functioning across four domains: Communication, Socialization, Daily Living, Fine Motor and Gross Motor skills. VABS also allows the calculation of a composite score (CS).

The Aberrant Behavior Checklist (ABC) was administered to caregivers to investigate the following domains: Irritability, Social Withdrawal, Stereotypic Behavior, Hyperactivity/Noncompliance, and Inappropriate Speech (Farmer & Aman, 2017).

Child Behavior Checklist (CBCL) is one of the most widely used reports of children's emotional and behavioral problems and is derived from parent-based interviews. It consists of six DSM-oriented scales assessing, on a scale from 0 to 2, affective problems, anxiety, ADHD, oppositional and conduct problems, and somatic problems. The CBCL is aimed at children between 18 and 60 months of age. Along with scores for the seven syndromic subscales, it provides a total score and two factors, namely externalization and internalization (Ebesutani et al., 2010).

The Clinical Global Impression Scale (CGI), an instrument assessing the clinician view of the patient global functioning, was employed at T2. The CGI is composed of two separated scales, one measuring the overall improvement since the start of treatment, and one measuring the severity of symptoms (Busner & Targum, 2007).

The Quantitative-Checklist for Autism in Toddlers (Q-Chat) is a screening tool for autistic symptoms in children 18-24 months. It assesses the following domains on a 5-point scales: shared play, social communication, shared attitude, stereotypical behavior, language development and sensory interests (Allison et al., 2008).

The Quality of Life in Autism Questionnaire (QoLA) is a standardized instrument created to assess the quality of life of parents of children 2-18 y.o. with ASD. It comprises two scales, one designed to specifically investigate the parent's quality of life, while the other is parent report on how problematic their child autistic symptoms are (Eapen et al., 2014).

The brief version of the World Health Organization Quality of Life Assessment (WHOQoL) was also administered. This instrument assesses the quality of life across four domains: physical, mental, social and health (WHOQOL Group, 1998).

Repetitive behaviors were evaluated through Repetitive Behavior Scale-Revised (RBS-R), a questionnaire composed of five subscales: Ritualistic/Sameness Behavior, Stereotypic Behavior, Self-injurious Behavior, Compulsive Behavior, and Restricted Interests (Bodfish et al., 2000).

The Short Sensory Profile (SSP) is a caregiver questionnaire designed to identify sensory processing anomalies and associated behavioral and emotional responses. It includes the following domains: Tactile Sensitivity, Taste/Smell Sensitivity, Movement Sensitivity, Under Responsive/Seeks Sensation, Auditory Filtering, Low Energy/Weak and Visual/Auditory Sensitivity (McIntosh et al., 1999).

The Social Responsiveness Scale (RSR) is a short questionnaire that measures the severity of autistic social impairments across five domains, notably Social Awareness, Social Cognition, Social Communication, Social Motivation and Mannerisms. It consists of 65 items to be scored on a Likert scale from 0 to 3 points, referring to the child's behavior over the past 6 months (Bölte, Poustka & Constantino, 2008).

Visual Analogue Scales (VAS) were also employed. VAS are frequently used in clinical research to measure the intensity or frequency of several characteristics and/or symptoms. It consists of a straight horizontal line, at the end of which are the two extremes of the condition to be measured. The patient (or the evaluator) is asked to indicate on the line the point that best corresponds to his/her condition or severity symptoms (Klimek et al., 2017). In the present study, VAS were used to evaluate severity of autistic symptoms on sixteen areas, namely Socio-Emotion skills, Non-Verbal skills, Expressive Language, Receptive Language, Theory of Mind, Stereotypy, Restricted Interests, Rigidity, Sensory Processing, Imitation, Joint Attention, Play, Play with Others, Holding Objects, Fine Motor skills and Gross Motor skills, on a 10-point scale.

A set of early social skills, such as eye contact, imitation, joint attention and play skills, were also assessed during a semi-structured play session conducted at first visit by the child psychiatrist. The assessment tool place before the decision to send each child for behavioral treatment. Measures were coded as follows:

- *Eye Contact*: normal, inconsistent, absent/very rare.
- *Imitation*: present, absent.
- *Joint Attention*: complete, incomplete, absent.
- *Play Skills*: disorganized play, manipulative/object play, imitation play, pretend play.

3.2.4 Data Analysis

First, to categorize children as Full, Partial or Low Responders to ESDM, the magnitude of change in ADOS-2 and GMDS-ER scores between T0 and T2 was calculated. This was done by estimating a Delta, as follows: [(T2-T0/T0*100)]. Eight children included in our sample were part of a previous research protocol, which involved the administration of GMDS-ER at T0 and T2, and ADOS-2 at T0

only. For this reason, in addition to the "GMDS-ER+ADOS-2" criterion, the clinical judgment based on the DSM-5 was also used to delineate the response profiles of all children.

The three response profiles identified are:

- *Full responders*: children whose score no longer exceed ADOS-2 cut-off, or who no longer meet DSM-5 criteria for ASD according to clinician evaluation, and whose GMDS-ER scores improve by more than 25% on at least four subscales, including Language and Personal-Social domains.
- *Partial responders*: children who improve their ADOS-2 total score by at least 25%, but still exceeding the cut-off, and who improve their GMDS-ER scores by more than 25% in 2/3 domains.
- *Low responders*: children who improve by less than 25% on ADOS-2 total score, and who improve by 25% in one area, or less than 25% in several areas, on GMDS-ER.

Paired one-tailed *t*-tests were performed to compare children's pre- and post-intervention scores on ADOS-2, GMDS-ER, PEP-3 and VABS scales. We made this choice because we had a specific hypothesis about the direction of the effect, notably that children would improve, and not worsen, in these skills at the end of the ESDM. When dependent variables were not normally distributed, as indicated by Shapiro-Wilks test, paired one-tailed Wilcoxon Tests were performed instead.

Detection of univariate outliers was also conducted, based on the percentiles. Suspected outliers were considered those observations that lay outside the interval formed by the 2.5 and 97.5 percentiles.

To identify predictors of treatment outcomes, a series of logistic regressions were conducted, with "response to treatment" as our three-level (Low, Partial and Full) categorical dependent variable, and children's intake measures as independent variables. These measures were chosen among those more frequently reported in the Literature to predict children's response to behavioral treatments.

Logistic regressions are often used to estimate the probability that a patient will present a certain outcome from clinical baseline characteristics that are thought to be related to that outcome, and this probability is expressed as odds ratio (OR) (Tolles & Meurer, 2016). Specifically, logistic regressions allow the calculation of odds, i.e., the ratio between the probability of an event happening and the probability of that event not happening. The change in the odds of an outcome because of its association with a particular event is measured as a ratio of odds, namely OR (*ibidem*). An OR <1 indicate a negative relationship between predictor and outcome, while an OR > 1 indicate a positive relationship between predictor and outcome.

Since our outcome was an ordinal variable, we performed several simple ordinal logistic regressions. Ordinal logistic regression basically indicates what the probability is of belonging to a higher category, and this probability is expressed as OR. When the proportional regression assumption for

ordinal logistic regression (i.e., that the odds ratio is the same across categories; Brant, 1990) was violated, a multinomial logistic regression was performed instead. In this case, one reference category is compared to each other categories.

To test the goodness of fit of our models, we compared each fitted model (i.e., the one with a predictor) against the null model (i.e., a nested model where no predictors are included and thus where the coefficient = 0) via asymptotic likelihood ratio tests. If the *p*-value attributed to this comparison is < 0.05, the fitted model explains better than the null model the variability of the outcome. As an additional measure of goodness of fit of the model, Nagelkerke Pseudo R^2 for each fitted model were also calculated. Although Pseudo R^2 are not directly comparable to the coefficient of determination (R^2) in linear regression models, they are still commonly used to measure the power of explanation of the model (Faraway, 2006).

When our independent variable was categorical and not metrical, we performed Fisher's exact test (Fisher, 1970), which allows to test the null of independence of data in a contingency table and is recommended with small sample size such as ours (Freeman & Campbell, 2007). Since contingency tables in our case had more than two rows and two columns, Bonferroni-corrected pairwise technique was also applied.

All statistical analysis were performed in R, version 4.2.0 (R Core Team, 2022).

3.3 Results

3.3.1 ESDM outcome at a group level

First, we evaluated whether the treatment had been effective at a group level. We compared children's means scores of the main measures at T0 and T2, notably ADOS-2, GMDS-ER, PEP-3 and VABS subscales and total scores, by performing paired one-tailed *t*-tests. Shapiro-Wilks tests showed that not all our variables were normally distributed, therefore in those cases we performed one-tailed Wilcoxon Test for paired samples. Results of all paired one-sample *t*-test and Wilcoxon Test are listed in Table 9.

We found a significant decrease in children's ADOS-2 Total score, indicating an overall improvement in core autistic symptoms after nine months of ESDM. Looking at ADOS-2 subscales, significant decrease from pre- to post-intervention were found in the ADOS-2 SA, but not in the ADOS-2 RRB, indicating that children improved especially in the social-affect domain, but not in the restricted and repetitive behaviors. Significant increase from T0 to T2 were also found in GMDS-ER GQ and PEP-3 CVP scores, representative of an improvement in cognitive skills after the ESDM. Children

achieved significant gains in VABS Daily Living. No significant differences were found in all other GMDS-ER, PEP-3 and VABS subscales from pre- to post-treatment.

Table 9. Pre- to post-treatment scores.

	Pre-treatment			Post-treatment			Nominal *p*-values
	N	Mean (SD)	Range	*N*	Mean (SD)	Range	
ADOS-2 Total score	24	17.83 (4.78)	9-30	24	15.67 (5.12)	6-23	0.02*
ADOS-2 SA	24	14.96 (3.75)	8-20	24	12.96 (4.71)	3-19	0.01*
ADOS-2 RRB	24	2.88 (2.19)	0-10	24	2.71 (1.27)	0-5	0.36
GMDS-ER GQ	32	60.8 (17.73)	21-100	32	65.29 (17.89)	43-111	0.04*
GMDS-ER Locomotor	32	69.31 (21.13)	24-124	32	73.25 (17.08)	20-105	0.88
GMDS-ER Personal/Social	32	53.83 (17.22)	19-99	32	59.69 (21.15)	15-109	0.02*
GMDS-ER Language	32	45.34 (18.26)	14-103	32	50.15 (27.00)	11-136	0.13
GMDS-ER Visuomotor Coordination	32	61.63 (20.11)	17-103	32	64.75 (19.44)	16-110	0.15
GMDS-ER Performance	31	71.09 (25.69)	26-146	32	75.81 (26.01)	17-125	0.19
PEP3 CVP	25	55.84 (18.37)	32-110	24	67.11 (22.38)	40-123	0.02*
PEP-3 EL	25	43.36 (8.78)	22-65	24	47.44 (18.98)	25-83	0.20
PEP-3 RL	25	49.28 (14.57)	22-79	24	56.01 (24.47)	23-120	0.14
PEP-3 FM	25	65.92 (17.14)	44-100	24	65.61 (11.35)	44-88	0.70
PEP-3 GM	25	67.2 (17.16)	44-103	24	67.64 (16.25)	25-90	0.63
PEP-3 VMI	25	61.4 (17.38)	36-100	24	63.36 (15.02)	38-93	0.53
VABS CS	24	66.33 (12.07)	42-88	23	65.00 (13.8)	31-92	0.63
VABS Communication	24	64.58 (12.17)	34-89	23	58.7 (22.2)	20-93	0.92
VABS Social Skills	24	63.92 (13.78)	30-86	23	68.2 (10.7)	41-92	0.09
VABS Daily Living	24	63.25 (24.5)	20-90	23	71.6 (14.8)	21-93	0.05*

Significant comparisons are marked with as asterisk (*).
ADOS: Autism Diagnostic Observation Schedule; CS: Composite Score; CVP: Cognitive Verbal-Preverbal; EL: Expressive Language; FM: Fine Motor; GM: Gross Motor; GMDS-ER: Griffith Mental Developmental Scale - Extended Revised; GQ: Global Quotient; PEP: Psychoeducational Profile; RL: Receptive Language; RRB: Repetitive and Restricted Behaviors SA: Social Affect; VABS: Vineland Adaptive Behavior Scale; VMI: Visuo-motor Imitation.

3.3.2 Response profile to ESDM

As expected, we found great interindividual variability in response to treatment. According to the criteria delineated in the "Data Analysis" section, at the end of the ESDM the response profile of each child was identified. We compared the scores obtained on GMDS-ER (n = 32) subscales and on ADOS-2 (n = 24) at T0 and T2, by means of Delta calculation, and evaluated the areas in which an improvement of more than 25% was present. Results are displayed in Table 10.

First, we evaluated the magnitude of change on GMDS-ER subscales from baseline to post-treatment. Four (12.5%) children achieved an improvement of > 25% in 4 or more GMDS-ER subscales, including Persona-Social and Language domains, and thus were considered FRs to GMDS-ER. Eight (25%) children improved by more than 25% in 4 areas, including only one between Personal-Social and Language domain, or in 2-3 areas, and were considered PRs according to GMDS-ER. The remaining children (n = 20, 62.5%) were LRs, since they achieved an improvement of > 25% only in one or none of GMDS-ER subscales. Of all 32 children, six (18.75%) displayed an overall GQ > 70 at intake: 4 were among the LRs, one was a FR and one a PR.

Regarding ADOS-2 Total score, 2 (8.3%) children were FRs, since they no longer exceeded the cut-off for ASD at the end of treatment, and 6 (18.75%) were PRs, because they improved by > 25%, but still exceeding the cut-off. The remaining 16 (66.6%) children were LR to ADOS-2.

The criterion "GMDS-ER+ADOS-2" was compared to the clinical judgment based on DSM-5, which was also needed in establishing the response profile of those children who lacked the ADOS-2 score at T2, and for whom a Delta could not be calculated (n = 8). In 22 out of 24 cases, the "GMDS-ER+ADOS-2" criterion and the clinical judgement matched. In the remaining cases, children achieved significant improvement only in one of GMD-ER subscales, one in language (GMDS-ER Language Delta: 81.55) and one in the motor domain (GMDS-ER Locomotor Delta: 31.03), whereas on ADOS-2 Total score the improvement was not sufficient to be classified as PR (Delta was -7.69 in one case, and -16.67 in the other). Nevertheless, according to the clinical judgement, these children considerably benefited from the ESDM, and thus were classified as PRs (see Table 10).

Overall, the final treatment response profiles across children in our sample were as follows: four (12.5%) Full Responders, 8 (25%) Partial Responders, and 20 (62.5%) Low Responders (see Figure 3).

Table 10. Delta of GMDS-ER subscales (n = 32) and ADOS-2 Total score (n = 24), and final response profile of each child according to the clinical judgment (n = 32).

LEGEND
Low responders
Partial responders
Full responders

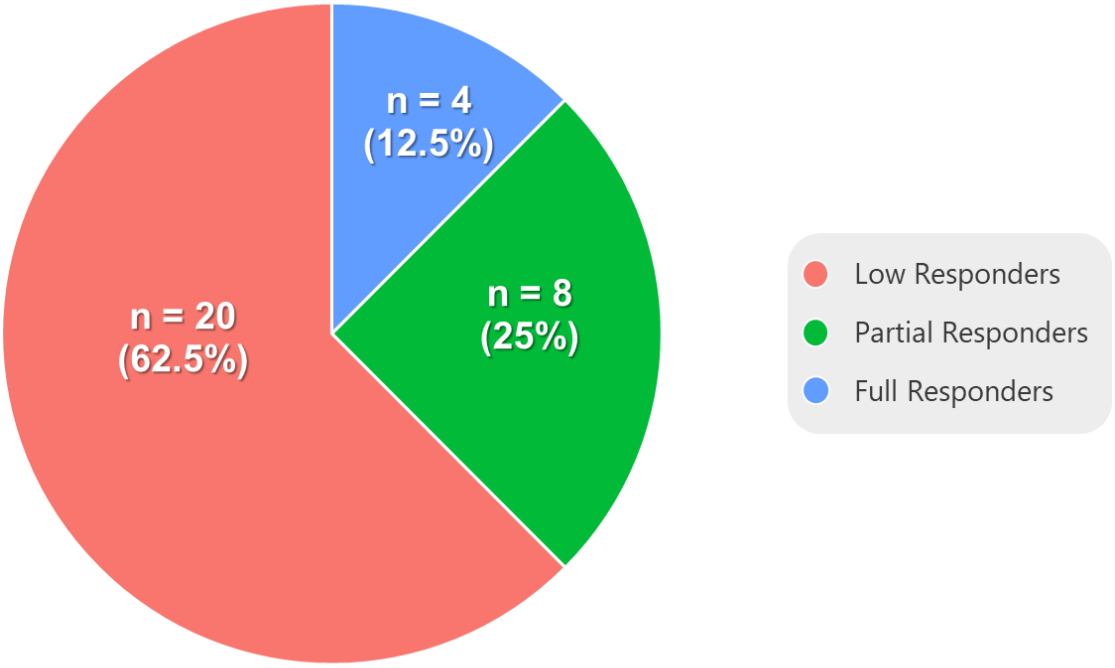
Patient (name's initial)	Delta GMDS-ER Locomotor %	Delta GMDS-ER Personal-Social %	Delta GMDS-ER Language %	Delta GMDS-ER Visuomotor Coordination %	Delta GMDS-ER Performance %	Delta GMDS-ER GQ %	Delta ADOS-2 Total score %	Clinical Judgment DSM-5
A.L.	1.72	9.26	-26.09	3.08	2.94	0.00	0.00	Low Responder
G.M.	19.23	-8.33	68.97*	83.33*	114.63*	58.33*	--	Low Responder
B.L.	-20.51	-48.08	9.76	-28.85	-30.16	-25.86†	--	Low Responder
B.V.	10.94	21.95	-9.76	1.56	-2.74	7.14	--	Low Responder
H.L.	-20.83	-13.16	5.36	-13.64	25.00	-4.88	--	Low Responder
L.A.	118.75*	-9.21	90.7*	-13.92	21.69	24.24	--	Full Responder
P.G.	44.26*	41.56*	61.90*	61.76*	59.74*	52.05*	--	Full Responder
V.F.	14.81	32*	53.13*	61.76*	158.82*	62.86*	--	Partial Responder
A.G.	-13.68	34.55*	-60.19	-13.59	--	-20.00†	--	Low Responder
C.L.	-10.05	3.54	17.50	6.82	-6.30	0.00†	-33.33*	Full Responder
G.M.	-71.43	-68.65	-75.00	-68.63	-81.52	-25.81	0.00	Low Responder
P.G.	-8.35	-8.11	-14.88	-14.66	-26.09	-14.29†	25.00	Low Responder
P.A.	-31.45	10.58	81.55*	-17.50	-14.38	-8.16†	-7.69	Partial Responder

Patient (name's initial)	Delta GMDS-ER Locomotor %	Delta GMDS-ER Personal-Social %	Delta GMDS-ER Language %	Delta GMDS-ER Visuomotor Coordination %	Delta GMDS-ER Performance %	Delta GMDS-ER GQ %	Delta ADOS-2 Total score %	Clinical Judgment DSM-5
V.G.	-13.87	33.56*	87.50*	32.72*	6.03	17.82	-31.25*	Partial Responder
T.M.	113.96*	141.79*	-21.43	170.59*	150.00*	104.76*	-36.67*	Partial Responder
D.L.	-0.72	-2.03	-12.58	-4.76	13.39	-1.94	-22.73	Low Responder
P.G.	9.59	11.15	-3.56	9.03	-12.05	5.85	72.73	Low Responder
S.S.	45.44*	20.62	116.67*	32.95*	0.14	32.6*	7.14	Low Responder
S.L.	7.14	12.24	-10.31	2.74	50.00*	12.24	25.00	Low Responder
D.G.	6.67	13.21	-25.53	3.17	31.60*	3.17	-21.05	Low Responder
C.L.	0.00	19.57	2.50	96.67*	38.30*	26.67*	-40.00*	Partial Responder
P.P.	58.62*	110.53*	64.29*	37.50*	17.46	52.00*	-50.00*	Partial Responder
B.M.	-10.39	14.29	89.29*	-10.98	6.49	7.81	-57.14*	Full Responder
G.C.	-6.25	-24.19	-39.58	-3.17	-29.23	-25.00	9.52	Low Responder
P.G.	-27.63	126.32*	-44.83	16.67	-9.38	2.13	9.52	Low Responder
R.F.	27.27*	6.52	-17.02	0.00	6.82	4.35	-23.81	Low Responder
T.G.	47.37*	56*	87.80*	10.00	13.64	40.74*	-33.33*	Partial Responder
T.S.	38.98*	25.58*	-21.05	15.38	0.00	14.00	10	Low Responder
B.R.	28.3*	-6.38	26.67*	-11.90	-2.08	-16.67	-19.05	Low Responder
S.A.	31.03*	19.67	6.85	20.29	-15.12	8.70	-16.67	Partial Responder
C.D.	-10.87	-29.63	-29.27	-22.03	-28.99	-22.68	-5.26	Low Responder
B.F.	50.00*	5.17	0.00	-17.57	12.35	10.58	-13.04	Low Responder

*improvement of > 25 %; † GQ at intake > 70.

ADOS: Autism Diagnostic Observation Schedule; DSM: Diagnostic and Statistical Manual of Mental Disorders; GMDS-ER: Griffith Mental Developmental Scale - Extended Revised; GQ: Global Quotient.

Figure 3. Rates of Full, Partial and Low responders (n = 32).



3.3.3 Predictors of response to ESDM

Once the response profile of each child was established, we were interested in identifying behavioral and developmental characteristics collected at baseline that would help us predict children subsequent response to treatment. Based on the results of our systematic review and meta-analysis (Chapter 2, Table 7), we hypothesized that response profile would be primarily predicted by: social skills, communication and language skills, cognitive abilities. We also took into account other characteristics that have been reported to be positive predictors of ESDM outcome in Literature, although less consistently, namely age at treatment start, autism severity, and adaptive behaviors at intake. Finally, we tested for the predictive power of skills considered pivotal in the ESDM framework, that is, joint attention, imitation, eye contact, and play skills.

Pre-treatment measures collected at T0 included in our analyses were: ADOS-2 (SA, RRB and Total score), ADI-R (A: social interaction, B: communication, C: restricted, repetitive, and stereotyped patterns of behavior, D: anomalies in the development before 36 months), DSM-5 severity levels, GMDS-ER (GQ, Personal-Social, Language, Visuomotor Coordination, Performance), PEP-3 (Cognitive Verbal-Preverbal, Expressive Language, Receptive Language, Visual-Motor Imitation),

VABS (Communication, Daily Living, Socialization, Motor and Composite score), chronological age at intake, eye contact, joint attention, imitation and play skills.

Before proceeding with our analyses, we checked for univariate outliers. Some suspected outliers were detected; nevertheless, we decided not to remove them from our dataset, as these observations were not due to measurement or sampling errors, but rather were legitimate values that are a natural component of the population we are investigating.

Our analyses show that positive response to ESDM is significantly associated with the following intake children characteristics: joint attention, cognitive abilities (but not DQ), personal-social skills, stereotyped and repetitive mannerism, communication skills, receptive and expressive language, visuo-motor imitation. No significant results were found with regard to overall autism severity, age at intake, adaptive behaviors, imitation, eye contact and play skills.

Estimates, coefficients, and *p*-values of significant models are reported in Table 12. Significant results are depicted below.

Table 12. Estimates, coefficients, statistics and *p*-values of Fisher's Exact Test and logistic regression analyses of significant predictors of outcome.

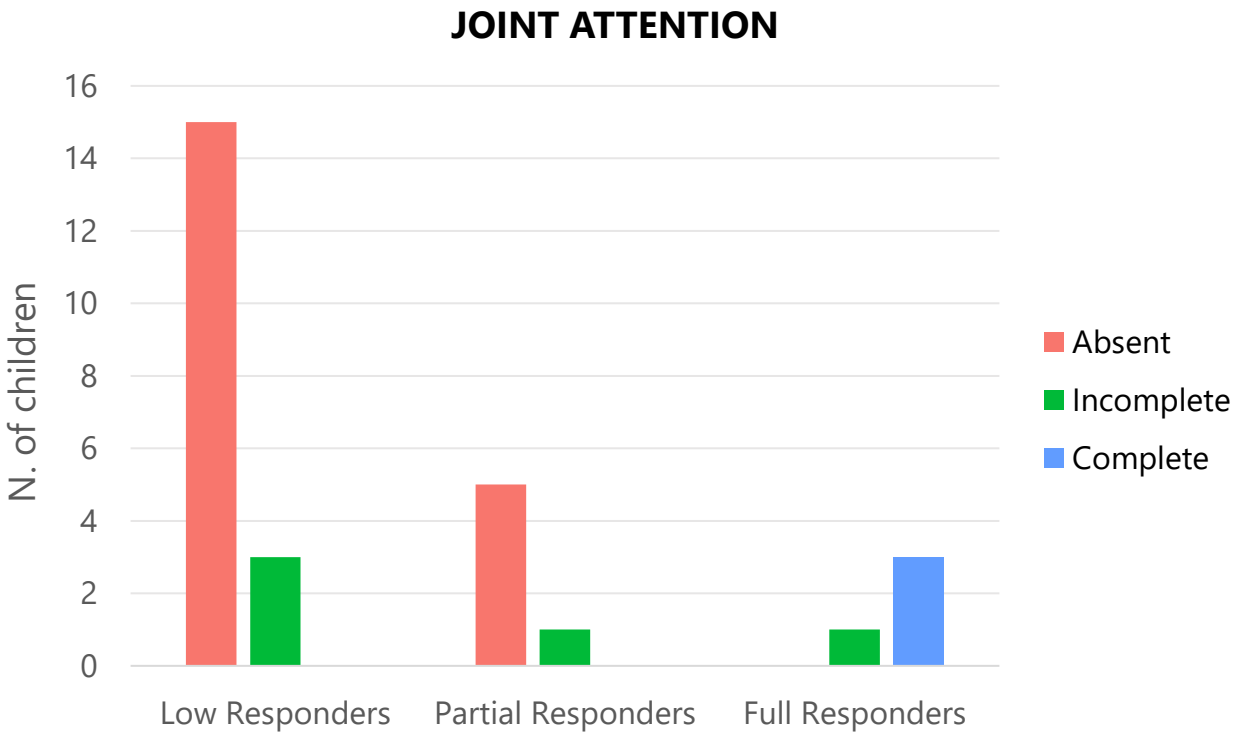
		Overall goodness of fit							
	N	χ^2	*p*	Nagelkerke pseudo R2	*b*	SE B	*z*	*p*	OR (CI)
1. Joint Attention	28	---	0.002	---	---	---	---	0.01	---
2. PEP-3 CVP	25	8.99	0.003	0.38	0.08	0.03	2.65	0.008	1.08 (1.03-1.15)
3. ADI-R C3	25	8.85	0.003	0.37	-1.57	0.63	-2.50	0.01	0.20 (0.05-0.61)
4. GMDS-ER Personal-Social	32	9.80	0.007	0.31	0.13	0.06	2.14	0.03	1.13 (1.01-1.27)
5. VABS Communication	24	6.52	0.010	0.29	0.12	0.05	2.09	0.04	1.13 (1.02-1.29)
6. PEP-3 EL	25	6.17	0.012	0.27	0.14	0.06	2.24	0.02	1.15 (1.03-1.31)
7. PEP-3 RL	25	5.87	0.015	0.26	0.08	0.03	2.24	0.03	1.08 (1.01-1.16)
8. ADI-R C Total	25	5.66	0.02	0.25	-0.42	0.2	-2.08	0.04	0.66 (0.42-0.94)
9. PEP-3 VMI	25	4.75	0.029	0.22	0.06	0.03	2.04	0.04	1.06 (1.00-1.13)

ADI-R: Autism Diagnostic Interview-Revised; CI: Confidence Interval; CVP: Cognitive Verbal/Preverbal; EL: Expressive Language; GMDS-ER: Griffith Mental Developmental Scale – Extended Revised; OR: Odd Ratio; PEP: Psychoeducational Profile; RL: Receptive Language; SE: Standard Error; VMI: Visuo-motor Imitation.

Joint Attention. Fisher's exact test on joint attention across the three response profiles yielded significant results (p = 0.002). Pairwise Bonferroni-corrected test indicated that the significant difference was in LRs vs. FRs (p = 0.01). Indeed, children with complete joint attention at intake were those children who responded most positively to ESDM, while children who were categorized as LR mostly lacked joint attention (see Figure 4).

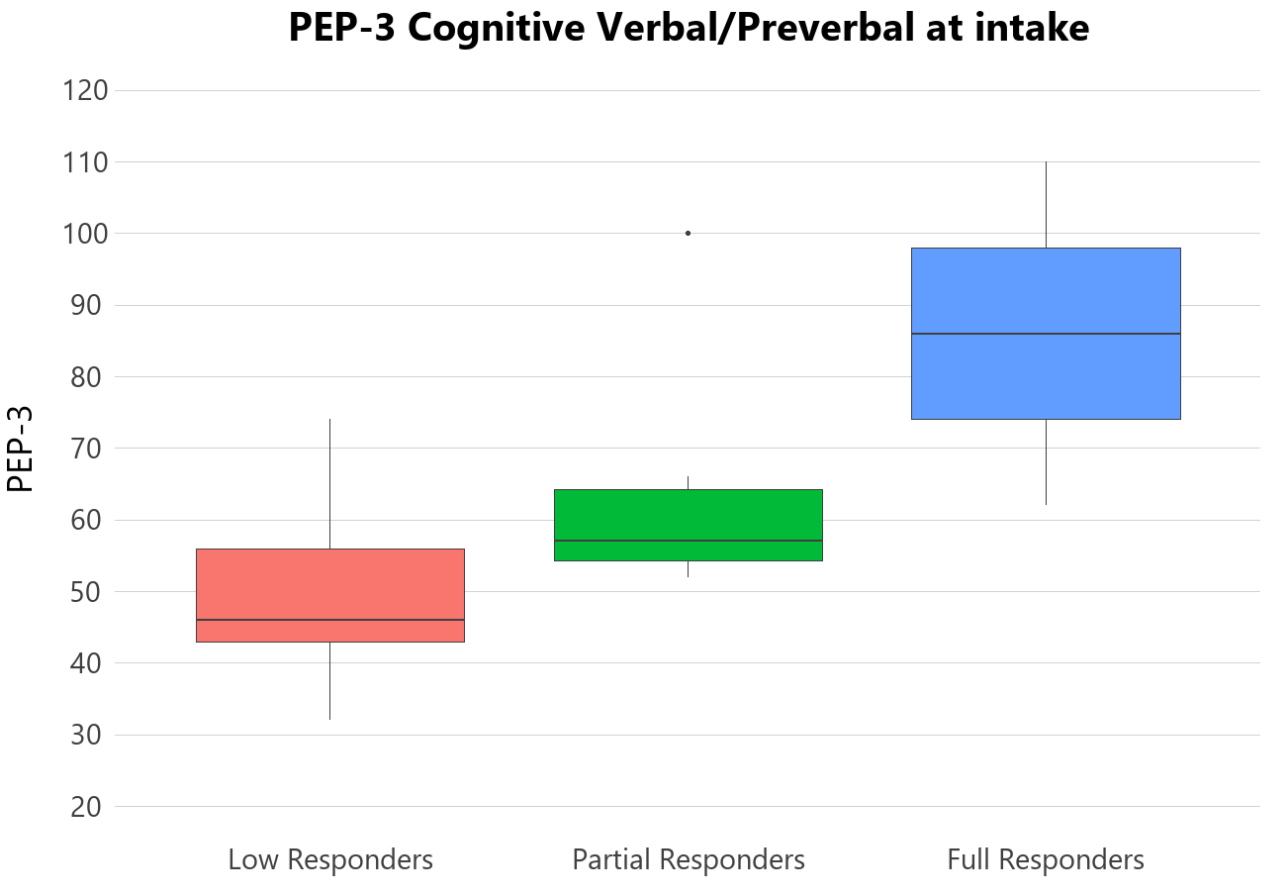
Figure 4. Pre-treatment joint attention in LR, PR and FR.

Complete: the child looks in the direction of pointing and then looks back and makes eye contact.
Incomplete: the child looks in the direction of pointing but does not look back and does not make eye contact.
Absent: the child does not look in the direction of pointing.



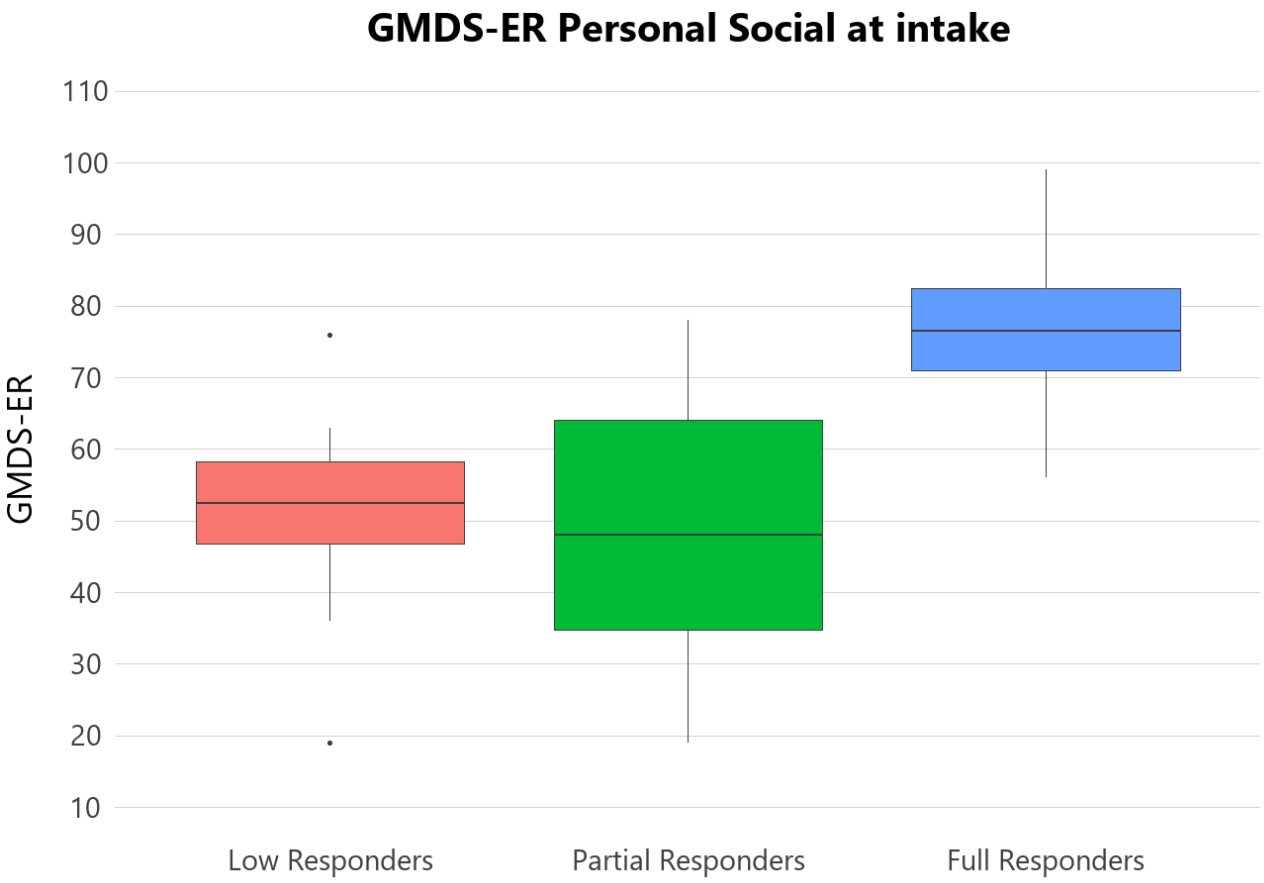
PEP-3 Cognitive Verbal-Preverbal. Children cognitive abilities significantly predicted positive response to ESDM. Comparison of the ordinal logistic regression model with and without coefficient showed that the first one fit better (χ^2 = 8.99, p = 0.003). Children with higher cognitive skills at intake were 1.08 times more likely to be FRs than PRs or LRs (p = 0.008; see Figure 5).

Figure 5. Pre-treatment PEP-3 Cognitive Verbal-Preverbal scores in LR, PR and FR.



GMDS-ER Personal Social. Brant test revealed that proportional assumption for ordinal logistic regression did not hold ($p = 0.01$) and therefore a multinomial logistic regression was conducted. This model yielded significant results, showing that children with higher GMDS-ER Personal Social scores at intake had 1.13 times the odds of being FRs than LRs ($p = 0.03$; see Figure 6). Comparison of the model with and without coefficient showed that the first one fit better ($\chi^2 = 9.80$, $p = 0.007$).

Figure 6. Pre-treatment GMDS-ER Personal/Social scores in LR, PR and FR.

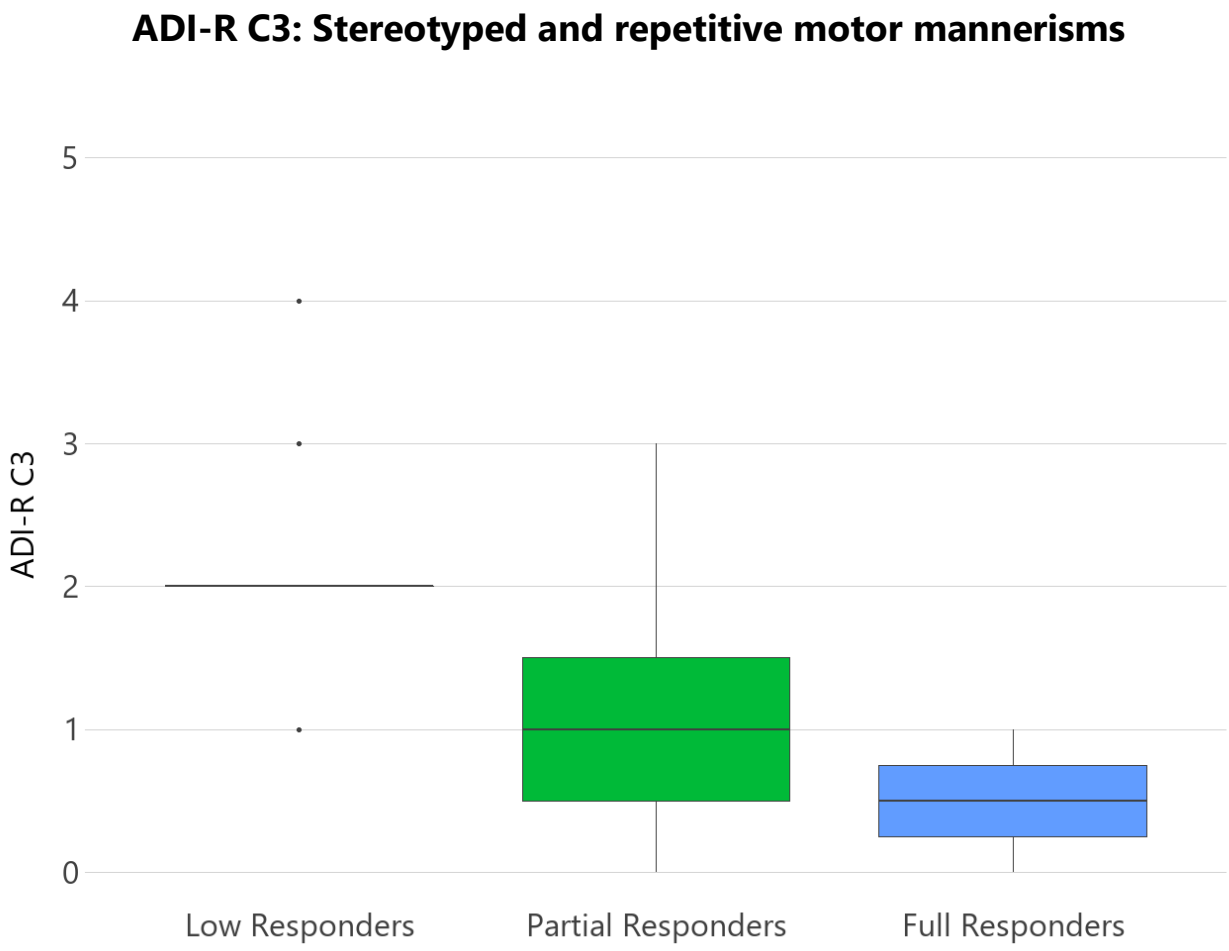


ADI-R C. Lower repetitive and stereotyped patterns of behaviors significantly predicted a positive response to ESDM. Ordinal logistic regression showed that for every additional point on ADI-R C, the odds of being FRs decrease of 0.66 (p = 0.04). This implies that FRs obtained lower scores on ADI-R C at intake than did LRs and PRs, reflecting lower repetitive and stereotyped patterns of behaviors at baseline (see Figure 7).

Figure 7. Pre-treatment ADI-R C scores in LR, PR and FR.

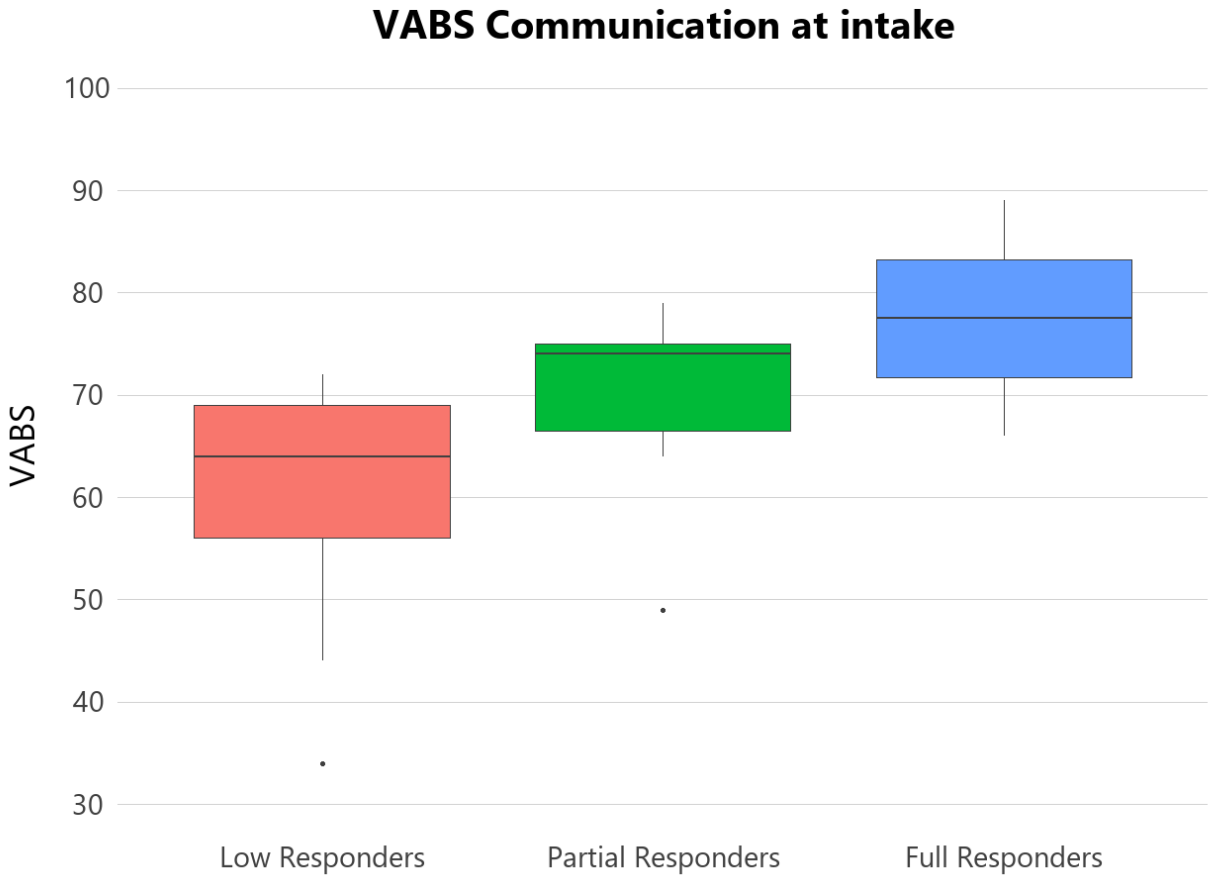
Specifically, this significance appears to be due to ADI-R C3 subscale, measuring stereotyped and repetitive motor mannerisms, since this was the only ADI-R C (and ADI-R in general) subscales where FRs scored significantly lower than LRs and PRs (p = 0.01, OR: 0.2; see Figure 8). Comparison of the fitted model against the null model showed that the fitted model fit better in both ADI-R C and ADI-R C3 cases (ADI-R C: χ^2 = 6.52, p = 0.01; ADI-R C3: χ^2 = 8.85, p = 0.00).

Figure 8. Pre-treatment ADI-R C3 scores in LR, PR and FR.



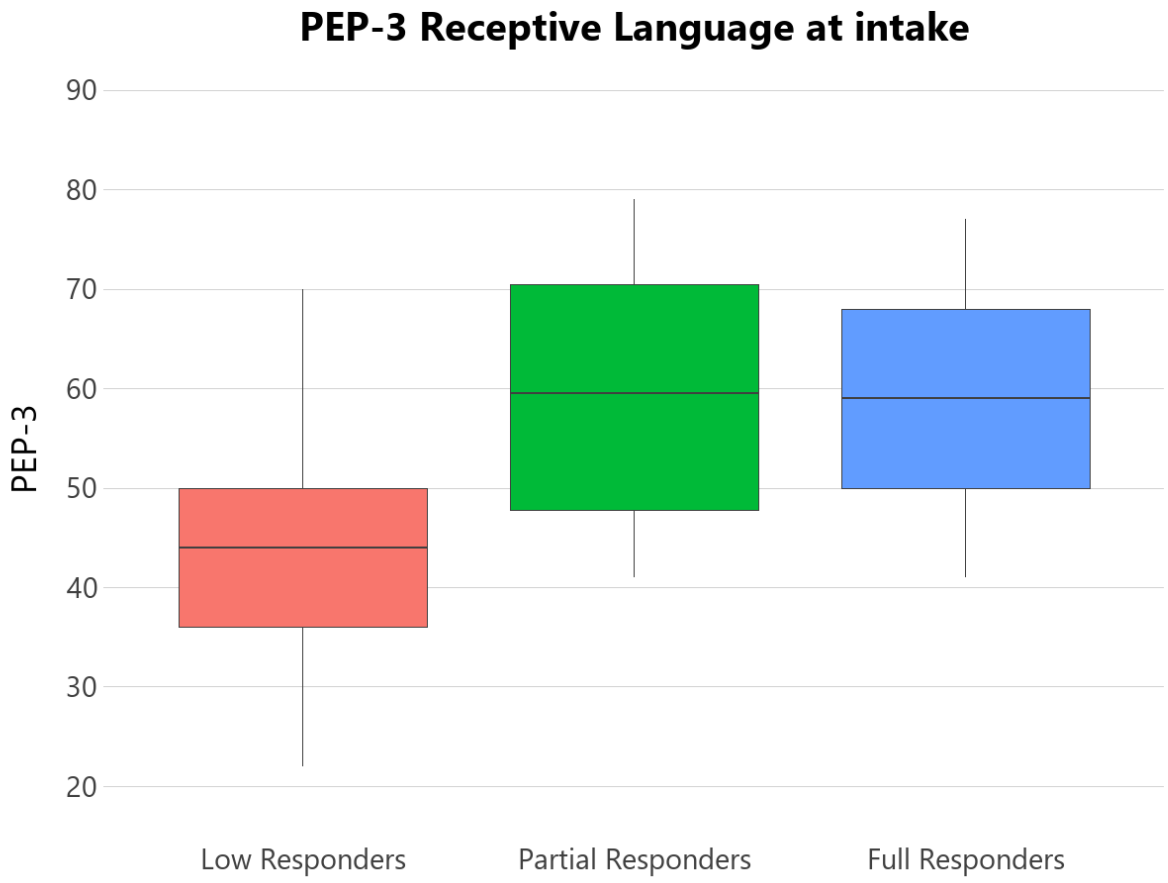
VABS Communication. Comparison of the fitted model against the null model showed that the first one fit better (χ^2 = 6.52, p = 0.01). The association between positive response to ESDM and communication skills was significant (p = 0.04). Children with higher communication skills at intake had 1.13 times the odds of being FRs, rather than PRs or LRs (see Figure 9).

Figure 9. Pre-treatment VABS Communication scores in LR, PR and FR.



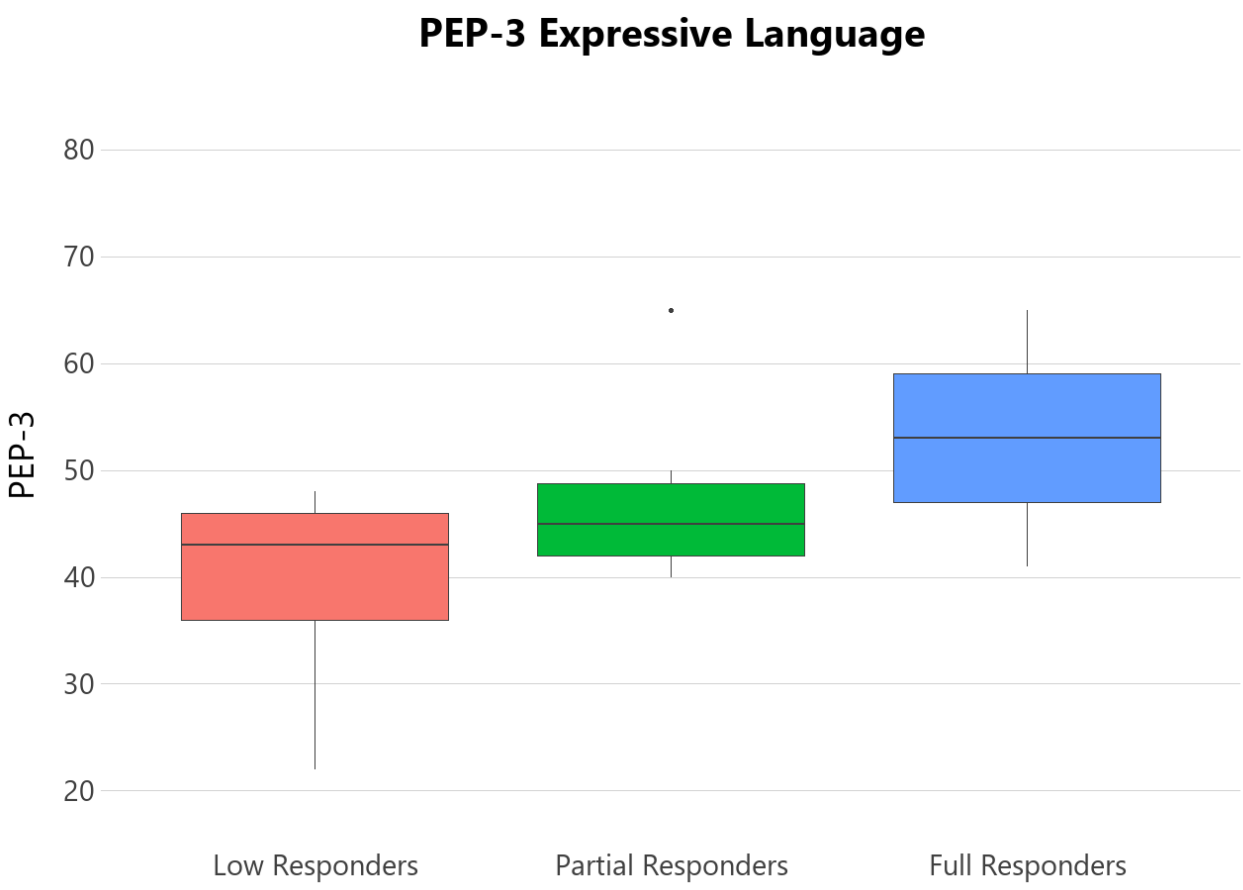
PEP-3 Receptive Language. Comparison of the fitted model against the null model showed that the first one fit better (χ^2 = 5.87, p = 0.02). Receptive language skills significantly predicted treatment response: children with higher scores in PEP-3 RL at intake had 1.08 times the odds of being FRs, rather than PRs or LRs (p = 0.03; see Figure 10).

Figure 10. Pre-treatment PEP-3 Receptive Language scores in LR, PR and FR.



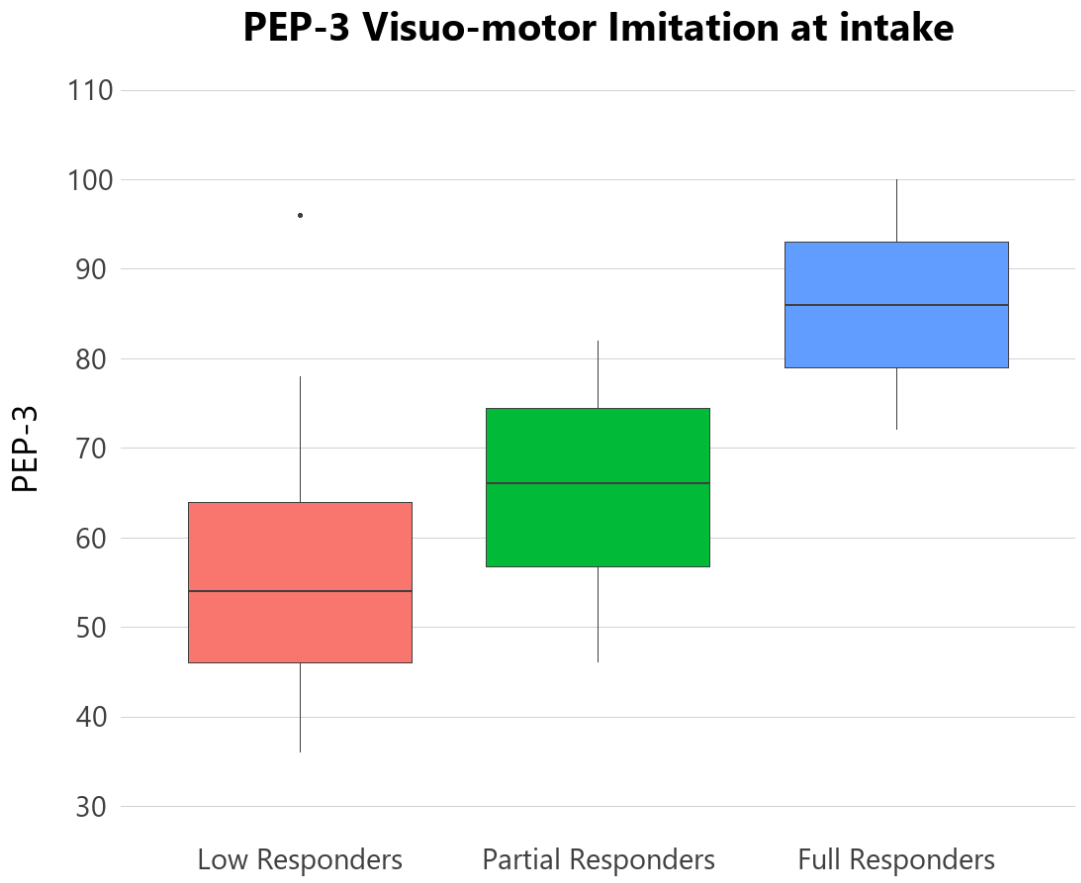
PEP-3 Expressive Language. Expressive language skills were also predictors of children positive outcome. Comparison of the fitted model against the null model showed that the first one fit better (χ^2 = 6.17, p = 0.01). For children with higher PEP-3 EL scores at baseline, the odds of being FRs, rather than PRs or LRs, was 1.15 higher, and this probability was significant (p = 0.02; see Figure 11).

Figure 11. Pre-treatment PEP-3 Expressive Language scores in LR, PR and FR.



PEP-3 Visuo-motor imitation. Comparison of the fitted model against the null model showed that the first one fit better ($\chi^2 = 4.75$, $p = 0.03$). The ordinal logistic regression revealed that PEP-3 VMI was a significant predictor of children response to ESDM. Specifically, children who scored higher in PEP-3 VMI were 1.06 times more likely of being FRs than PRs or LRs ($p = 0.04$; see Figure 12).

Figure 12. Pre-treatment PEP-3 Visuo-motor Imitation scores in LR, PR and FR.



Chapter 4.
General discussion and conclusions

One of the ultimate aims of autism research is to allow for clinicians to define "which treatment for which child" beforehand, based on clinical predictors and objective biomarkers (genetics, brain imaging, electrophysiology, eye tracking, etc.). This aim not only regards pharmacological therapy (Cucinotta et al., 2020; Vorstman et a., 2014), but also behavioral interventions which, although sharing some common elements, differ significantly in multiple aspects of their methodology. Structured behavioral approaches tend to favor a "teaching" relationship, and employ tasks which preferentially request and strengthen cognitive skills, making broader use of extrinsic motivators (Landa, 2018); naturalistic approaches employ a "playground-like" relationship, employing activities that leave greater freedom of choice to the child and act as intrinsic motivators, while primarily requiring and strengthening social cognition (eye contact, theory of mind, joint attention, empathy, etc.). Predictably, not all children respond equally well to early intervention approaches, and yet it is at this time, early in life, that it would be most useful to provide targeted treatments, to maximally exploit neural plasticity.

Research on pretreatment predictors of greater gains after behavioral interventions is still in its infancy. The available evidence trying to link preferential response to a specific type of treatment with a set of clinical/demographic characteristics is even more incomplete. The present work sought to begin to fill the gaps in this area of research, mainly in two ways. First, a systematic review and meta-analysis was conducted to systematize the results of the Literature published to date on predictors of response to two major evidence-based treatments, namely EIBI and ESDM. Then, we carried out an experimental longitudinal study on predictors of positive response in 32 young children receiving individualized ESDM for nine months.

We collected all peer-reviewed published studies on EIBI and ESDM investigating behavioral and developmental factors as predictors of treatment response in children under 48 months at intake. As depicted in section 2.4, we assessed the number of studies that examined the association between a given putative predictor and post-treatment outcome, and how many reported a positive association. To better systematize data, we calculated a cumulative *p*-value for each significant predictor, combining reported statistical outcomes from multiple studies using Fisher's method.

Predictors of positive response to EIBI and ESDM partially overlap, but also display some interesting differences. As expected, IQ/DQ was the most frequently reported variable associated with response to EIBI, but an association was also found in ESDM studies, although this was not as strong (Table 7). This difference is also present in studies involving older children (see Supplementary Tables 3 and 6, respectively for EIBI and ESDM studies). Conversely, response to ESDM was often associated with a set of variables falling within the realm of "social cognition", including more speech-related

sounds (i.e., greater intention to communicate), better receptive and expressive language, and greater attention to faces (Tables 6 and 7). Some of these "social" variables also partly predict response to EIBI, but not quite as convincingly (Table 7). On the one hand, the overlap is not surprising, because both EIBI and ESDM propose tasks whose learning is influenced by child IQ/DQ, and both require interpersonal interactions between child and therapist. On the other hand, these results are collectively beginning to delineate an important difference: IQ/DQ and social cognition may represent preferential predictors of response to EIBI vs. ESDM, respectively, because these functions are the most required by each approach and may benefit the most from each approach. More specifically, children who have better cognitive functions, systemizing skills, and visuo-spatial IQ may benefit more from structured approaches that largely employ these functions, whereas children endowed with greater social motivation and with milder deficits in social cognition and communication may benefit more from approaches that use play, child's initiative and fun interactions as a primary channel for stimulation. At the same time, EIBI and ESDM may catalyze global development and broader adaptive skills by primarily strengthening cognitive and social functions, respectively. Nonetheless, given the available evidence, this statement must be viewed more as a rationale hypothesis with some promising initial support than as a firm conclusion, which will require additional research.

There is some evidence that children may benefit more from starting interventions at an earlier age, especially for ESDM (Table 6). However, results are mixed and perhaps even disappointing for EIBI (Tables 4 and 7). Some researchers (Contaldo et al., 2020; Vivanti et al., 2016) suggest that this might be due to the very narrow age-range of the children enrolled in most studies. However, even studies with a wider age-range have reported variable results, with more EIBI than ESDM studies finding that younger children achieve better results (see Supplementary Tables 3 and 6, for EIBI and ESDM studies, respectively). Efficacy also in slightly older children suggests that the critical period of maximum plasticity, allowing for a satisfactory response to any type of early intensive intervention for some children could conceivably last longer than the narrow time-window adopted in this review (i.e., for some children, even starting treatment at 4–5 years of age may foster a positive response). At the same time, this lack of consistent benefits in children whose treatment was started at a very early age clearly shows that there are other variables that can override the effect of age on neuroplastic responses to environmental stimulation. One of these variables could conceivably be represented by rare (Cucinotta et al., 2020) and common (Lamb et al., 2015) genetic variants that negatively modulate dendritic spine formation and synaptic functions, including LTP and LTD.

Similarly, mixed results were obtained with autism severity in both EIBI and ESDM, investigated in three and six studies, respectively (Tables 3 and 6). Milder symptoms at treatment onset were only associated with better outcome in 1/3 (33.3%) EIBI studies and in 1/6 (16.6%) ESDM studies here

reviewed (Table 7), although studies recruiting older children have yielded more positive results, especially with ESDM (see Supp. Tables 3 and 6). This apparently greater predictive power for ESDM, if not a chance finding, may indicate that the severity of autistic symptoms is less relevant and predictive when treatment is started early, but may begin to matter more as treatment is started in children 4 years or older.

The methodological rigor of the studies included in this review was assessed through the Critical Review Form for Quantitative Studies (Law et al., 1998), which highlighted several limitations, such as a small sample size yielding interesting trends, which often did not reach statistical significance (e.g., Cohen, Amerine-Dickens & Smith, 2006; Smith, Groen & Wynn, 2000), lack of a comparison group receiving another treatment, and lack of randomized assignment to intervention. Only two out of thirteen studies on EIBI and three out of nine studies on ESDM were fully RCTs. In some cases, the treatment protocol was not described in sufficient detail, including its intensity and duration. Studies did not always clearly report the time elapsed between the first assessment and the start of treatment, making it difficult to define the actual age of children at the beginning of the intervention. In some studies, the clinical and psycho-diagnostic assessment was made a few months after the start of treatment (Latrèche et al., 2021). Different instruments were used to measure the same variable, such as IQ and language skills, sometimes even within the same study, thus preventing a true comparison of the results. The use of objective measures such as gaze parameters obtained using eye-tracking technologies has been very limited, at least in young children (Latrèche et al., 2021). Some important functions, such as imitation and joint attention, were investigated in very few studies. This is especially surprising, since it has been suggested that these skills may be predictors of positive response to ESDM, given its focus on social and communication skills (Laister et al., 2021). This insufficient number of studies does not stem from a bias introduced by our inclusion criteria, because very few studies involving also older children have investigated these critical functions (Laister et al., 2021; Lewon & Ghezzi, 2021; Vivanti et al., 2013). On the contrary, it would be advisable to shift away from broader constructs, such as IQ and language skills, and toward more proximal predictors of outcome, such as spontaneous imitation, vocalizations, and social interaction (Vivanti et al., 2014*a*). Furthermore, investigators often find what they are searching for: as an example, proportionally fewer ESDM studies investigated IQ/DQ as predictor of treatment outcome compared to EIBI studies (7/11 studies = 63.6% for ESDM, as compared to 11/13 studies = 84.6% of EIBI studies). Several studies have found that "overall pre-treatment functioning" or "initial learning rate" are associated with later outcome (Goin-Kochel et al., 2007; Préfontaine et al., 2022; Smith, Klorman & Mruzek, 2015; Virues-Ortega, Rodríguez, & Yu, 2013; Weiss, 1999), and this may lead to circular reasoning: children who are more likely to learn because they are skillful will learn more and sooner

from interventions (Vivanti et al., 2014*a*). However, many other factors and confounding variables may influence the initial rate of learning, for example, the degree of response to reinforcers used during treatment (Weiss, 1999). Moreover, early intensive interventions should act as catalyzers of functions which, at a given time, are observed to be underdeveloped in a child: placing this process into the framework of a mere "learning" paradigm may well be oversimplifying the complexities of motivation, emotion and relationship, which are at the core of autistic deficits. This point is often neglected in studies whose outcome measures are exclusively focused on cognitive functioning and DQ. Hopefully, future research will take these limitations into account, to reach broader and more definitive conclusions (Howlin, Magiati & Charman, 2009; Waddington, van der Meer, Sigafoos, 2016; Weiss, 1999).

Once systematized results from the Literature, our next step was to carry out one experimental longitudinal research to investigate behavioral and developmental predictors of outcomes in an Italian sample of autistic toddlers receiving individualized ESDM for nine months. Informed by results from the systematic review and meta-analysis, our main hypothesis was that children's outcome would be primarily explained by intake socio-communicative skills and language abilities. Furthermore, based on the ESDM framework, we hypothesized that ESDM response would also be predicted by joint attention, imitation skills, eye contact and play skills.

First of all, our results showed that, at a group level, participants significantly improved in DQ and overall verbal/preverbal cognitive abilities, personal-social skills and core autistic symptoms, especially social impairments. Children also displayed a global improvement in adaptive behaviors, as reflected by an increase in VABS Daily Living scores from T0 to T2. However, no significant difference was found in language and communication scores from pre- to post-treatment. Interestingly, ADOS-2 SA and Total score significantly decreased from baseline to post-intervention. This is noteworthy, since studies have not often found a significant decrease in ADOS scores, at least in ADOS composite score, even in the face of an improvement in symptom severity from a clinical perspective (Devescovi et al., 2016; Vivanti et al., 2016; Vivanti et al., 2019).

Since we did not include a control group, we cannot rule out that children would have improved regardless of the treatment they received. Nonetheless, our results are in line with previous studies showing that ESDM is effective in enhancing young autistic children developmental trajectory (e.g., Dawson et al., 2010; Rogers et al., 2019; Vivanti et al., 2016), even if administered in a less intensive way (= 6 hr per week, e.g., Colombi et al., 2018; Contaldo et al., 2020; Devescovi et al., 2016).

We found great interindividual variability in ESDM outcome. Based on the magnitude of change in GMDS-ER subscales scores and ADOS-2 Total score, four (12.5%) children were categorized as Full

Responders, eight (25%) as Partial Responders and 20 (62.5%) as Low responders. The four FRs lost ASD diagnosis after nine months of ESDM, according to ADOS-2 Total score and DSM-5 criteria. PRs significantly improved in ADOS-2 Total scores from baseline to post-intervention, although their scores were still above the cut-off for ASD. Lastly, LRs symptoms severity remained stable across the nine months.

We were especially interested in identifying factors that might help us predict children response to ESDM. Putative predictors were chosen among those variables that were found to be more reliably related to ESDM outcome in our systematic review, namely social skills, expressive and receptive language, communication abilities and cognitive skills. We also investigated other factors that were found to be associated with ESDM response, although less consistently, notably age at intake, autism severity, repetitive and stereotyped behaviors, adaptive behaviors. Finally, we evaluated whether early social skills such as eye contact, joint attention, imitation and play skills would predict ESDM outcome in our sample. These last three variables were each examined only in one of the 11 ESDM studies reviewed in Chapter 2, and all yielded non-significant results. Nonetheless, these skills are pivotal for learning, and the ESDM is especially developed to boost joint attention and imitation as the "social infrastructures" for the acquisition of new skills (Rogers, Vivanti & Rocha, 2017). For this reason, we hypothesized that children who start out already advantaged in these skills may be more likely to respond positively to ESDM.

Several factors were found to significantly predict children's outcome. In line with our hypothesis, joint attention was consistently associated to the most positive response to ESDM. Indeed, all children who displayed complete joint attention at intake were categorized as FRs at post-treatment, and most of the children who lacked joint attention at baseline were LRs (Figure 3). Instead, we found no significant association between treatment outcome and eye contact, plays skills and imitation. Although these results are contrary to what we expected, they reflect what has already been found in the Literature (Contaldo et al., 2020; Rogers et al., 2019).

DQ was the second most reported predictor in ESDM studies reviewed in Chapter 2. Our findings partially replicated this result: children with higher PEP-3 CVP before treatment start were more likely to be FRs. Moreover, in our sample full response was also associated with greater visuo-motor abilities at intake, as measured by PEP-3 VMI. This factor has rarely been investigated as predictor of treatment outcome, but one study found it to be associated with treatment response (Hayward et al., 2009). Nevertheless, overall DQ as assessed by GMDS-ER did not predict ESDM response in our sample. This result is hard to explain, since there is evidence that PEP-3 CVP developmental level is comparable to IQ as measured by other instruments (De Giacomo et al., 2016).

Children response to ESDM was also significantly predicted by levels of repetitive and stereotyped pattern of behaviors, especially motor mannerism. This variable has not been associated with treatment outcome frequently, but it was found to be a significant predictor in two out of three ESDM studies in our systematic review (Godel et al., 2022; Wang et al., 2022). However, these studies administered ADOS-2 RRB to measure this factor, and in our sample only ADI-R C intake scores, but not ADOS-2 RRB, were associated with later response to treatment. Both ADI-R and ADOS-2 investigate several aspects of the broader domain of repetitive and stereotyped behaviors, and in our case only one of these was found to be a predictor of a positive response, notably repetitive and stereotyped motor mannerisms. ADOS-2 offers a single RRB score, while ADI-R assigns a score to each of these subdomains. This is probably the reason why only ADI-R, specifically ADI-R C3 and ADI-R C total, but not ADOS-2 RRB, led to significant results.

Social skills were significantly associated with positive treatment outcome, although only GMDS-ER Personal Social, and not VABS Socialization, were significant predictors of response.

Our findings confirmed the importance of communication and language skills in predicting response to ESDM. Children who scored higher on VABS Communication, and on PEP-3 EL and PEP-3 RL subscales, were more likely to benefit the most from ESDM. Interestingly, VABS Communication and PEP-3 EL pre-treatment scores among the three response groups follows an upward trend, with FRs scoring the highest, LRs scoring the lowest, and PRs scoring somewhere in between (Figure 9 and 10). On the contrary, for PEP-3 RL, FRs and PRs obtained overlapping score (Figure 11). This data suggests that starting treatment with receptive language skills may be sufficient to show at least some response to ESDM, while for a full response, having developed good communication and expressive language skills may be required.

Some of the findings that emerged from our systematic review and meta-analysis were not replicated in our study. For instance, younger age at treatment start did not affect response to ESDM ($b = 0.08$; $p = 0.32$). This finding may seem counterintuitive to what has been said so far about the importance of early interventions, not least because several studies have found that younger children respond better to treatment (e.g., Devescovi et al., 2016; Harris & Handleman, 2000; MacDonald et al., 2014; Perry et al., 2011; Robain et al., 2020; Vivanti et al., 2016; Vivanti et al., 2019). However, our results could be explained by the very narrow range of age of children in our sample. Indeed, studies on predictors of treatment outcome including only children under 48 months at intake did not always find chronological age to be associated with treatment response (e.g., Contaldo et al., 2020; Hayward et al., 2009; Lovaas, 1987; Remington et al., 2007; Zitter et al., 2021).

We also assessed if autism severity measured with ADOS-2 and ADI-R was associated with treatment response. Except for the stereotyped and repetitive behavior domain, as already discussed, our

analyses yielded nonsignificant results. This was not unexpected, as four out of five ESDM studies reviewed in Chapter 2 reported similar results. Moreover, the only study finding a correlation between autism severity and treatment response did not use ADOS-2 as a measure of autism severity.

The effect of autism severity on ESDM outcome was also investigated through a Fisher's exact test on DSM-5 diagnostic categories and the three response profiles. This analysis yielded significant result ($p = 0.002$), suggesting that these two variables may not be independent. Nevertheless, this result did not survive to Bonferroni post-hoc analysis. Overall, these findings suggest that milder autism severity is not necessarily associated with a positive response to ESDM, at least in children entering treatment before 48 months of age (see Suppl. Table 6).

Finally, no significant result was found with regard to any of the VABS subscales, except for the Communication domain. Adaptive behaviors have been rarely investigated as predictors of ESDM outcomes, and even more rarely they have been found to be associated with treatment response. Our study does not seem to deviate from this trend.

Our experimental study presents some limitations. First, the three response groups were highly unbalanced, and this may have affected our results. To overcome this problem and to simplify the study design and analyses, we could have merged PRs and FRs into one single "Responders" group and compared it with LRs. However, we decided not to proceed in this way, because we believe that children which turned out to be PRs and FRs are not analogous. Indeed, PRs achieved significant gains after nine months of ESDM, but yet they remained on the autistic spectrum. In contrast, FRs improved to such an extent that at the end of treatment they no longer met ADOS-2 and DSM-5 diagnostic criteria for ASD.

To investigate the association between intake measures and ESDM response, several single logistic regressions, mainly ordinal, were performed. Ordinal logistic regression is a useful statistical method for predicting patients' outcome from their baseline characteristics; however, its validity depends on the number and suitability of the independent variables included, and the estimates of the effects of these variables on the outcome may be affected by possible collinearity (Tolles & Meurer, 2016). Some of the variables that were found to be significant predictors of ESDM response in our sample were indeed correlated, and for this reason we decided not to perform multiple logistic regression models including all significant predictors, but only single ones.

We investigated the predictive power of measures, notably ADOS-2 and GMDS-ER, that were related to the outcome of interest, since they were used as criteria to outline the three response categories. However, for this purpose we used the magnitude of change from baseline to post-treatment, and not the raw data, which instead is what was used as predictor of response. Consequently, results of regression models with these measures as independent variable should not be invalidated.

Children in our sample made significant gains at a group level, especially in the core autistic symptoms and cognitive domains. Nonetheless, since we did not include a control group receiving another kind of early intervention, these improvements cannot be ascribed to ESDM with certainty. This study remains exploratory in nature, and the results obtained should be interpreted with caution. Notwithstanding, our findings are consistent with those reported by studies conducted in a more controlled fashion, substantiating the results emerged from our systematic review and meta-analysis.

The present thesis was carried out with the purpose of systematizing Literature evidence on behavioral and developmental predictors of EIBI and ESDM outcome, and to complement them with new data from an experimental study on this topic. Despite its limitations and the need to further develop this topic, our results indicate that there are intrinsic behavioral and developmental characteristics that affect children response to treatment, and that at least some of these factors may be preferential predictors of response to one specific type of treatment. Specifically, evidence from the Literature suggests that higher pretreatment developmental quotient represents the strongest predictor of positive response to EIBI, while a set of socio-communication skills including intention to communicate, receptive and expressive language, and attention to faces, most consistently predicts response to ESDM. In line with these findings, results from our experimental study confirm that greater pre-treatment communication skills, including receptive and expressive language, are associated with a positive response to ESDM, together with joint attention, imitation and less stereotypic behaviors. This knowledge may be helpful to families and practitioners in choosing the most effective intervention for each child.

References

Allison, C., Baron-Cohen, S., Wheelwright, S., Charman, T., Richler, J., Pasco, G., & Brayne, C. (2008). The Q-CHAT (Quantitative Checklist for Autism in Toddlers): a normally distributed quantitative measure of autistic traits at 18-24 months of age: preliminary report. *Journal of autism and developmental disorders*, *38*(8), 1414–1425. https://doi.org/10.1007/s10803-007-0509-7

American Psychiatric Association. (1980). *Diagnostic and Statistical Manual of Mental Disorders* (3rd ed.).

American Psychiatric Association. (2013). *Diagnostic and Statistical Manual of Mental Disorders: DSM-5, 5th ed*. https://doi.org/10.1176/appi.books.9780890425596

Anderson, D. K., Oti, R. S., Lord, C., & Welch, K. (2009). Patterns of growth in adaptive social abilities among children with autism spectrum disorders. *Journal of abnormal child psychology*, *37*(7), 1019–1034. https://doi.org/10.1007/s10802-009-9326-0

Anderson, S. R., Avery, D. L., DiPietro, E. K., Edwards, G. L., et al. (1987). Intensive home-based early intervention with autistic children. *Education and Treatment of Children*, *10*(4), 352–366

Aoki, Y., Cortese, S., & Tansella, M. (2015). Neural bases of atypical emotional face processing in autism: A meta-analysis of fMRI studies. *The world journal of biological psychiatry: the official journal of the World Federation of Societies of Biological Psychiatry*, *16*(5), 291–300. https://doi.org/10.3109/15622975.2014.957719

Bacon, E. C., Courchesne, E., Barnes, C. C., Cha, D., Pence, S., Schreibman, L., Stahmer, A. C., & Pierce, K. (2018). Rethinking the idea of late autism spectrum disorder onset. *Development and psychopathology*, *30*(2), 553–569. https://doi.org/10.1017/S0954579417001067

Baghdadli, A., Assouline, B., Sonié, S., Pernon, E., Darrou, C., Michelon, C., Picot, M. C., Aussilloux, C., & Pry, R. (2012). Developmental trajectories of adaptive behaviors from early childhood to adolescence in a cohort of 152 children with autism spectrum disorders. *Journal of autism and developmental disorders*, *42*(7), 1314–1325. https://doi.org/10.1007/s10803-011-1357-z

Bai, D., Yip, B. H. K., Windham, G. C., Sourander, A., Francis, R., Yoffe, R., Glasson, E., Mahjani, B., Suominen, A., Leonard, H., Gissler, M., Buxbaum, J. D., Wong, K., Schendel, D., Kodesh, A., Breshnahan, M., Levine, S. Z., Parner, E. T., Hansen, S. N., Hultman, C., … Sandin, S. (2019). Association of Genetic and Environmental Factors With Autism in a 5-Country Cohort. *JAMA psychiatry*, *76*(10), 1035–1043.https://doi.org/10.1001/jamapsychiatry.2019.1411

Baird, G., Simonoff, E., Pickles, A., Chandler, S., Loucas, T., Meldrum, D., & Charman, T. (2006). Prevalence of disorders of the autism spectrum in a population cohort of children in South Thames: The Special Needs and Autism Project (SNAP). *Lancet (London, England)*, *368* (9531), 210–215. https://doi.org/10.1016/S0140-6736(06)69041-7

Baker, E., & Stavropoulos, K. K. M. (2020). The effects of oxytocin administration on individuals with ASD: Neuroimaging and behavioral evidence. *Progress in molecular biology and translational science*, *173*, 209–238. https://doi.org/10.1016/bs.pmbts.2020.04.009

Bal, V. H., Fok, M., Lord, C., Smith, I. M., Mirenda, P., Szatmari, P., Vaillancourt, T., Volden, J., Waddell, C., Zwaigenbaum, L., Bennett, T., Duku, E., Elsabbagh, M., Georgiades, S., Ungar, W. J., & Zaidman-Zait, A. (2020). Predictors of longer-term development of expressive language in two independent longitudinal cohorts of language-delayed preschoolers with Autism Spectrum Disorder. *Journal of child psychology and psychiatry, and allied disciplines*, *61*(7), 826–835. https://doi.org/10.1111/jcpp.13117

Baribeau, D., & Anagnostou, E. (2022). Novel treatments for autism spectrum disorder based on genomics and systems biology. *Pharmacology & therapeutics*, *230*, 107939. https://doi.org/10.1016/j.pharmthera.2021.107939

Baumgartner, T., Heinrichs, M., Vonlanthen, A., Fischbacher, U., & Fehr, E. (2008). Oxytocin shapes the neural circuitry of trust and trust adaptation in humans. *Neuron*, *58*(4), 639–650. https://doi.org/10.1016/j.neuron.2008.04.009

Bayley, N. (1993). *Bayley Scales of Infant Development* (2nd ed.). Psychological Corporation

Bayley, N. (2006). *Bayley Scales of Infant and Toddler Development: Bayley-III* (3rd ed.). Harcourt Assessment

Beaudoin, A. J., Sébire, G., & Couture, M. (2019). Parent-mediated intervention tends to improve parent-child engagement, and behavioral outcomes of toddlers with ASD-positive screening: A randomized crossover trial. *Research in Autism Spectrum Disorders*, *66*, 101416. https://doi.org/10.1016/j.rasd.2019.101416

Bejarano-Martín, Á., Canal-Bedia, R., Magán-Maganto, M., Fernández-Álvarez, C., Cilleros-Martín, M. V., Sánchez-Gómez, M. C., García-Primo, P., Rose-Sweeney, M., Boilson, A., Linertová, R., Roeyers, H., Van der Paelt, S., Schendel, D., Warberg, C., Cramer, S., Narzisi, A., Muratori, F., Scattoni, M. L., Moilanen, I., Yliherva, A., … Posada de la Paz, M. (2020). Early Detection, Diagnosis and Intervention Services for Young Children with Autism Spectrum Disorder in the European Union (ASDEU): Family and Professional Perspectives. *Journal of autism and developmental disorders*, *50*(9), 3380–3394. https://doi.org/10.1007/s10803-019-04253-0

Bellani, M., Calderoni, S., Muratori, F., & Brambilla, P. (2013). Brain anatomy of autism spectrum disorders I. Focus on corpus callosum. *Epidemiology and psychiatric sciences*, *22*(3), 217–221. https://doi.org/10.1017/S2045796013000139

Ben-Itzchak, E., & Zachor, D. A. (2007). The effects of intellectual functioning and autism severity on outcome of early behavioral intervention for children with autism. *Research in developmental disabilities*, *28*(3), 287–303. https://doi.org/10.1016/j.ridd.2006.03.002

Ben-Itzchak, E., & Zachor, D. A. (2009). Change in autism classification with early intervention: Predictors and outcomes. *Research in Autism Spectrum Disorders*, *3*(4), 967-976. https://doi.org/10.1016/j.rasd.2009.05.001

Ben-Itzchak, E., & Zachor, D. A. (2011). Who benefits from early intervention in autism spectrum disorders?. *Research in Autism Spectrum Disorders*, *5*(1), 345-350. https://doi.org/10.1016/j.rasd.2010.04.018

Bent, C., Glencross, S., McKinnon, K. et al. Predictors of Developmental and Adaptive Behaviour Outcomes in Response to Early Intensive Behavioural Intervention and the Early Start Denver Model. J Autism Dev Disord (2023). https://doi.org/10.1007/s10803-023-05993-w

Bibby, P., Eikeseth, S., Martin, N. T., Mudford, O. C., & Reeves, D. (2001). Progress and outcomes for children with autism receiving parent-managed intensive interventions. *Research in developmental disabilities*, *22*(6), 425–447. https://doi.org/10.1016/s0891-4222(01)00082-8

Bodfish, J. W., Symons, F. J., Parker, D. E., & Lewis, M. H. (2000). *Repetitive Behavior Scale–Revised (RBS-R)* [Database record]. APA PsycTests. https://doi.org/10.1037/t17338-000

Bölte, S., Poustka, F., & Constantino, J. N. (2008). Assessing autistic traits: cross-cultural validation of the social responsiveness scale (SRS). *Autism research : official journal of the International Society for Autism Research*, *1*(6), 354–363. https://doi.org/10.1002/aur.49

Brant R. (1990). Assessing proportionality in the proportional odds model for ordinal logistic regression. *Biometrics*, *46*(4), 1171–1178

Broder-Fingert, S., Feinberg, E., & Silverstein, M. (2018). Improving Screening for Autism Spectrum Disorder: Is It Time for Something New?. *Pediatrics*, *141*(6), e20180965. https://doi.org/10.1542/peds.2018-0965

Busner, J., & Targum, S. D. (2007). The clinical global impressions scale: applying a research tool in clinical practice. *Psychiatry (Edgmont (Pa. : Township))*, *4*(7), 28–37

Calderoni, S., Billeci, L., Narzisi, A., Brambilla, P., Retico, A., & Muratori, F. (2016). Rehabilitative Interventions and Brain Plasticity in Autism Spectrum Disorders: Focus on MRI-Based Studies. *Frontiers in neuroscience*, *10*, 139. https://doi.org/10.3389/fnins.2016.00139

Caselli, M.C., Pasqualetti, P., Stefanini, S. (2007). *Parole e Frasi Nel «Primo Vocabolario Del Bambino». Nuovi Dati Normativi Fra i 18 e 36 Mesi e Forma Breve Del Questionario [Words and Sentences in the First Vocabulary of the Child: New Normative Data from 18 to 36 Months and Short Form of the Questionnaire].* Franco Angeli.

Chevallier, C., Kohls, G., Troiani, V., Brodkin, E. S., & Schultz, R. T. (2012). The social motivation theory of autism. *Trends in cognitive sciences*, *16*(4), 231–239. https://doi.org/10.1016/j.tics.2012.02.007

Cinar, O., & Viechtbauer, W. (2022). The poolr Package for Combining Independent and Dependent p Values. *Journal of Statistical Software*, *101*(1), 1–42. https://doi.org/10.18637/jss.v101.i01

Cohen, H., Amerine-Dickens, M., & Smith, T. (2006). Early intensive behavioral treatment: replication of the UCLA model in a community setting. *Journal of developmental and behavioral pediatrics: JDBP*, *27*(2 Suppl), S145–S155. https://doi.org/10.1097/00004703-200604002-00013

Colombi, C., Narzisi, A., Ruta, L., Cigala, V., Gagliano, A., Pioggia, G., Siracusano, R., Rogers, S. J., Muratori, F., & Prima Pietra Team (2018). Implementation of the Early Start Denver Model in an Italian community. *Autism: the international journal of research and practice*, *22*(2), 126–133. https://doi.org/10.1177/1362361316665792

Contaldo, A., Colombi, C., Pierotti, C., Masoni, P., & Muratori, F. (2020). Outcomes and moderators of Early Start Denver Model intervention in young children with autism spectrum disorder delivered in a mixed individual and group setting. *Autism: the international journal of research and practice*, *24*(3), 718–729. https://doi.org/10.1177/1362361319888344

Cucinotta, F., Ricciardello, A., Turriziani, L., Calabrese, G., Briguglio, M., Boncoddo, M., Bellomo, F., Tomaiuolo, P., Martines, S., Bruschetta, M., La Fauci Belponer, F., Di Bella, T., Colombi, C., Baccarin, M., Picinelli, C., Castronovo, P., Lintas, C., Sacco, R., Biederer, T., Kellam, B., … Persico, A. M. (2020). FARP-1 deletion is associated with lack of response to autism treatment by early start denver model in a multiplex family. *Molecular genetics & genomic medicine*, *8*(9), e1373. https://doi.org/10.1002/mgg3.1373

Dawson G. (2008). Early behavioral intervention, brain plasticity, and the prevention of autism spectrum disorder. *Development and psychopathology*, *20*(3), 775–803. https://doi.org/10.1017/S0954579408000370

Dawson, G., Ashman, S. B., & Carver, L. J. (2000). The role of early experience in shaping behavioral and brain development and its implications for social policy. *Development and psychopathology*, *12*(4), 695–712. https://doi.org/10.1017/s0954579400004089

Dawson, G., Carver, L., Meltzoff, A. N., Panagiotides, H., McPartland, J., & Webb, S. J. (2002). Neural correlates of face and object recognition in young children with autism spectrum disorder, developmental delay, and typical development. *Child development*, *73*(3), 700–717. https://doi.org/10.1111/1467-8624.00433

Dawson, G., Jones, E. J., Merkle, K., Venema, K., Lowy, R., Faja, S., Kamara, D., Murias, M., Greenson, J., Winter, J., Smith, M., Rogers, S. J., & Webb, S. J. (2012). Early behavioral intervention is associated with normalized brain activity in young children with autism. *Journal of the American Academy of Child and Adolescent Psychiatry*, *51*(11), 1150–1159. https://doi.org/10.1016/j.jaac.2012.08.018

Dawson, G., Rogers, S., Munson, J., Smith, M., Winter, J., Greenson, J., Donaldson, A., & Varley, J. (2010). Randomized, controlled trial of an intervention for toddlers with autism: the Early Start Denver Model. *Pediatrics*, *125*(1), e17–e23. https://doi.org/10.1542/peds.2009-0958

Dawson, G., Webb, S. J., & McPartland, J. (2005). Understanding the nature of face processing impairment in autism: insights from behavioral and electrophysiological studies. *Developmental neuropsychology*, *27*(3), 403–424. https://doi.org/10.1207/s15326942dn2703_6

De Giacomo, A., Craig, F., Cristella, A., Terenzio, V., Buttiglione, M., & Margari, L. (2016). Can PEP-3 Provide a Cognitive Profile in Children with ASD? A Comparison Between the Developmental Ages of PEP-3 and IQ of Leiter-R. *Journal of applied research in intellectual disabilities : JARID*, *29*(6), 566–573. https://doi.org/10.1111/jar.12216

Development of the World Health Organization WHOQOL-BREF quality of life assessment. The WHOQOL Group. (1998). *Psychological medicine*, *28*(3), 551–558. https://doi.org/10.1017/s0033291798006667

Devescovi, R., Monasta, L., Mancini, A., Bin, M., Vellante, V., Carrozzi, M., & Colombi, C. (2016). Early diagnosis and Early Start Denver Model intervention in autism spectrum disorders delivered in an Italian Public Health System service. *Neuropsychiatric disease and treatment*, *12*, 1379–1384. https://doi.org/10.2147/NDT.S106850

Domes, G., Heinrichs, M., Michel, A., Berger, C., & Herpertz, S. C. (2007). Oxytocin improves "mind-reading" in humans. *Biological psychiatry*, *61*(6), 731–733. https://doi.org/10.1016/j.biopsych.2006.07.015

Eapen, V., Crnčec, R., Walter, A., & Tay, K. P. (2014). Conceptualisation and development of a quality of life measure for parents of children with autism spectrum disorder. *Autism research and treatment*, *2014*, 160783. https://doi.org/10.1155/2014/160783

Ebesutani, C., Bernstein, A., Nakamura, B. J., Chorpita, B. F., Higa-McMillan, C. K., Weisz, J. R., & The Research Network on Youth Mental Health (2010). Concurrent Validity of the Child Behavior Checklist DSM-Oriented Scales: Correspondence with DSM Diagnoses and Comparison to Syndrome Scales. *Journal of psychopathology and behavioral assessment*, *32*(3), 373–384. https://doi.org/10.1007/s10862-009-9174-9

Eikeseth, S., Klintwall, L., Jahr, E., & Karlsson, P. (2012). Outcome for children with autism receiving early and intensive behavioral intervention in mainstream preschool and kindergarten settings. *Research in Autism Spectrum Disorders*, *6*(2), 829–835. https://doi.org/10.1016/j.rasd.2011.09.002

Eikeseth, S., Smith, T., Jahr, E., & Eldevik, S. (2002). Intensive behavioral treatment at school for 4- to 7-year-old children with autism. A 1-year comparison controlled study. *Behavior modification*, *26*(1), 49–68. https://doi.org/10.1177/0145445502026001004

Eikeseth, S., Smith, T., Jahr, E., & Eldevik, S. (2007). Outcome for children with autism who began intensive behavioral treatment between ages 4 and 7: a comparison controlled study. *Behavior modification*, *31*(3), 264–278. https://doi.org/10.1177/0145445506291396

Eldevik, S., Eikeseth, S., Jahr, E., & Smith, T. (2006). Effects of low-intensity behavioral treatment for children with autism and mental retardation. *Journal of autism and developmental disorders*, *36*(2), 211–224. https://doi.org/10.1007/s10803-005-0058-x

Eldevik, S., Hastings, R. P., Hughes, J. C., Jahr, E., Eikeseth, S., & Cross, S. (2010). Using participant data to extend the evidence base for intensive behavioral intervention for children with autism. *American journal on intellectual and developmental disabilities*, *115*(5), 381–405. https://doi.org/10.1352/1944-7558-115.5.381

Ellis Weismer, S., & Kover, S. T. (2015). Preschool language variation, growth, and predictors in children on the autism spectrum. *Journal of child psychology and psychiatry, and allied disciplines*, *56*(12), 1327–1337. https://doi.org/10.1111/jcpp.12406

Elsabbagh, M., Divan, G., Koh, Y. J., Kim, Y. S., Kauchali, S., Marcín, C., Montiel-Nava, C., Patel, V., Paula, C. S., Wang, C., Yasamy, M. T., & Fombonne, E. (2012). Global prevalence of autism and other pervasive developmental disorders. *Autism research: official journal of the International Society for Autism Research, 5(3)*, 160–179. https://doi.org/10.1002/aur.239

Estes, A., Munson, J., Rogers, S. J., Greenson, J., Winter, J., & Dawson, G. (2015). Long-Term Outcomes of Early Intervention in 6-Year-Old Children With Autism Spectrum Disorder. *Journal of the American Academy of Child and Adolescent Psychiatry*, *54*(7), 580–587. https://doi.org/10.1016/j.jaac.2015.04.005

Evans B. (2013). How autism became autism: The radical transformation of a central concept of child development in Britain. *History of the human sciences*, *26*(3), 3–31. https://doi.org/10.1177/0952695113484320

Faraway J.J. (2006). *Extending the linear models with R: Generalized linear, mixed effects and nonparametric regression models*. Chapman and Hall.

Farmer, C., Aman, M.G. (2021). *Aberrant Behavior Checklist*. In: Volkmar, F.R. (eds) Encyclopedia of Autism Spectrum Disorders. Springer, Cham. https://doi.org/10.1007/978-3-319-91280-6_1632

Fatemi, S. H., Halt, A. R., Realmuto, G., Earle, J., Kist, D. A., Thuras, P., & Merz, A. (2002). Purkinje cell size is reduced in cerebellum of patients with autism. *Cellular and molecular neurobiology*, *22*(2), 171–175. https://doi.org/10.1023/a:1019861721160

Fenske, E. C., Zalenski, S., Krantz, P. J., & McClannahan, L. E. (1985). Age at intervention and treatment outcome for autistic children in a comprehensive intervention program. *Analysis & Intervention in Developmental Disabilities*, *5*(1-2), 49–58. https://doi.org/10.1016/S0270-4684(85)80005-7

Fernandez, B. A., & Scherer, S. W. (2017). Syndromic autism spectrum disorders: moving from a clinically defined to a molecularly defined approach. *Dialogues in clinical neuroscience*, *19*(4), 353–371. https://doi.org/10.31887/DCNS.2017.19.4/sscherer

Fetit, R., Hillary, R. F., Price, D. J., & Lawrie, S. M. (2021). The neuropathology of autism: A systematic review of post-mortem studies of autism and related disorders. *Neuroscience and biobehavioral reviews*, *129*, 35–62. https://doi.org/10.1016/j.neubiorev.2021.07.014

Fisher, R. A. (1970). *Statistical Methods for Research Workers*. Oliver & Boyd

Fisher, R.A. (1932). *Statistical Methods for Research Workers, 4th edition*. Oliver and Boyd (Edinburgh)

Flanagan, H.E., Perry, A., Freeman, N.L. (2012). Effectiveness of Large-Scale Community-Based Intensive Behavioral Intervention: A Waitlist Comparison Study Exploring Outcomes and Predictors. *Research in Autism Spectrum Disorders*, *6*, 673–682. https://doi.org/10.1016/j.rasd.2011.09.011

Fountain, C., Winter, A. S., & Bearman, P. S. (2012). Six developmental trajectories characterize children with autism. *Pediatrics*, *129*(5), e1112–e1120. https://doi.org/10.1542/peds.2011-1601

Frazier, T. W., Klingemier, E. W., Anderson, C. J., Gengoux, G. W., Youngstrom, E. A., & Hardan, A. Y. (2021). A Longitudinal Study of Language Trajectories and Treatment Outcomes of Early Intensive Behavioral

Intervention for Autism. *Journal of autism and developmental disorders*, *51*(12), 4534–4550. https://doi.org/10.1007/s10803-021-04900-5

Freeman, B. J., Ritvo, E. R., Needleman, R., & Yokota, A. (1985). The stability of cognitive and linguistic parameters in autism: a five-year prospective study. *Journal of the American Academy of Child Psychiatry*, *24*(4), 459–464. https://doi.org/10.1016/s0002-7138(09)60565-3

Freeman, J. V., & Campbell, M. J. (2007). The analysis of categorical data: Fisher's exact test. *Scope*, *16*(2), 11-12

Fuller, E. A., & Kaiser, A. P. (2020). The Effects of Early Intervention on Social Communication Outcomes for Children with Autism Spectrum Disorder: A Meta-analysis. Journal of autism and *developmental disorders*, *50*(5), 1683–1700. https://doi.org/10.1007/s10803-019-03927-z

Fulton, E., Eapen, V., Crnčec, R., Walter, A., & Rogers, S. (2014). Reducing maladaptive behaviors in preschool-aged children with autism spectrum disorder using the early start denver model. *Frontiers in pediatrics*, *2*, 40. https://doi.org/10.3389/fped.2014.00040

Genovese, A., & Butler, M. G. (2020). Clinical Assessment, Genetics, and Treatment Approaches in Autism Spectrum Disorder (ASD). *International journal of molecular sciences*, *21*(13), 4726. https://doi.org/10.3390/ijms21134726

Geoffray, M. M., Denis, A., Mengarelli, F., Peter, C., Gallifet, N., Beaujeard, V., Grosmaitre, C. J., Malo, V., Grisi, S., Georgieff, N., Magnificat, S., & Touzet, S. (2019). Using ESDM 12 hours per week in children with autism spectrum disorder: feasibility and results of an observational study. *Psychiatria Danubina*, *31*(3), 333–339. https://doi.org/10.24869/psyd.2019.333

Gesell Institute of Child Development (2012). *Gesell Developmental Observation–Revised and Gesell Early Screener. Technical Report: Ages 3–6*

Godel, M., Robain, F., Kojovic, N., Franchini, M., Wood de Wilde, H., & Schaer, M. (2022). Distinct Patterns of Cognitive Outcome in Young Children With Autism Spectrum Disorder Receiving the Early Start Denver Model. *Frontiers in psychiatry*, *13*, 835580. https://doi.org/10.3389/fpsyt.2022.835580

Goin-Kochel, R. P., Myers, B. J., Hendricks, D. R., Carr, S. E., & Wiley, S. B. (2007). Early responsiveness to intensive behavioural intervention predicts outcomes among preschool children with autism. *International Journal of Disability, Development and Education*, *54*(2), 151-175. https://doi.org/10.1080/10349120701330404

Green, G., Brennan, L. C., & Fein, D. (2002). Intensive behavioral treatment for a toddler at high risk for autism. *Behavior modification*, *26*(1), 69–102. https://doi.org/10.1177/0145445502026001005

Griffiths, R. (1984). *The abilities of young children: A comprehensive system of mental measurement for the first eight years of life* (Revised Edition). A.R.C.I.D. Test Agency Limited

Griffiths, R. (1984). *The Abilities of Young Children: A Comprehensive System of Mental Measurement for the First Eight Years of Life* (Revised Edition) A.R.C.I.D. Test Agency Limited

Guastella, A. J., Mitchell, P. B., & Dadds, M. R. (2008). Oxytocin increases gaze to the eye region of human faces. *Biological psychiatry*, *63*(1), 3–5. https://doi.org/10.1016/j.biopsych.2007.06.026

Ha, S., Sohn, I. J., Kim, N., Sim, H. J., & Cheon, K. A. (2015). Characteristics of Brains in Autism Spectrum Disorder: Structure, Function and Connectivity across the Lifespan. *Experimental neurobiology*, *24*(4), 273–284. https://doi.org/10.5607/en.2015.24.4.273

Hansen, S. N., Schendel, D. E., Francis, R. W., Windham, G. C., Bresnahan, M., Levine, S. Z., Reichenberg, A., Gissler, M., Kodesh, A., Bai, D., Yip, B. H. K., Leonard, H., Sandin, S., Buxbaum, J. D., Hultman, C., Sourander, A., Glasson, E. J., Wong, K., Öberg, R., & Parner, E. T. (2019). Recurrence Risk of Autism in Siblings and Cousins: A Multinational, Population-Based Study. *Journal of the American Academy of Child and Adolescent Psychiatry*, *58*(9), 866–875. https://doi.org/10.1016/j.jaac.2018.11.017

Happé, F. G., Mansour, H., Barrett, P., Brown, T., Abbott, P., & Charlton, R. A. (2016). Demographic and Cognitive Profile of Individuals Seeking a Diagnosis of Autism Spectrum Disorder in Adulthood. *Journal of autism and developmental disorders*, *46*(11), 3469–3480. https://doi.org/10.1007/s10803-016-2886-2

Harris, S. L., & Handleman, J. S. (2000). Age and IQ at intake as predictors of placement for young children with autism: a four- to six-year follow-up. *Journal of autism and developmental disorders*, *30*(2), 137–142. https://doi.org/10.1023/a:1005459606120

Hayward, D., Eikeseth, S., Gale, C., & Morgan, S. (2009). Assessing progress during treatment for young children with autism receiving intensive behavioural interventions. *Autism : the international journal of research and practice*, *13*(6), 613–633. https://doi.org/10.1177/1362361309340029

Heil, K. M., & Schaaf, C. P. (2013). The genetics of Autism Spectrum Disorders--a guide for clinicians. *Current psychiatry reports*, *15*(1), 334. https://doi.org/10.1007/s11920-012-0334-3

Howard, J. S., Sparkman, C. R., Cohen, H. G., Green, G., & Stanislaw, H. (2005). A comparison of intensive behavior analytic and eclectic treatments for young children with autism. *Research in developmental disabilities*, *26*(4), 359–383. https://doi.org/10.1016/j.ridd.2004.09.005

Huguet, G., Benabou, M., & Bourgeron, T. (2016). The Genetics of Autism Spectrum Disorders. In P. Sassone-Corsi (Eds.) et. al., *A Time for Metabolism and Hormones*. (pp. 101–129). Springer

Jacquemont, S., Coe, B. P., Hersch, M., Duyzend, M. H., Krumm, N., Bergmann, S., Beckmann, J. S., Rosenfeld, J. A., & Eichler, E. E. (2014). A higher mutational burden in females supports a "female protective model" in neurodevelopmental disorders. *American journal of human genetics*, *94*(3), 415–425. https://doi.org/10.1016/j.ajhg.2014.02.001

Jeste, S. S., Varcin, K. J., Hellemann, G. S., Gulsrud, A. C., Bhatt, R., Kasari, C., Wu, J. Y., Sahin, M., & Nelson, C. A., 3rd (2016). Symptom profiles of autism spectrum disorder in tuberous sclerosis complex. *Neurology*, *87*(8), 766–772. https://doi.org/10.1212/WNL.0000000000003002

Kanner, L. (1943). Autistic disturbances of affective contact. *Nervous Child*, *2*, 217–250

Kaplan, G., & McCracken, J. T. (2012). Psychopharmacology of autism spectrum disorders. *Pediatric clinics of North America*, *59*(1), 175–xii. https://doi.org/10.1016/j.pcl.2011.10.005

Kasari, C., Gulsrud, A., Freeman, S., Paparella, T., & Hellemann, G. (2012). Longitudinal follow-up of children with autism receiving targeted interventions on joint attention and play. *Journal of the American Academy of Child and Adolescent Psychiatry*, *51*(5), 487–495. https://doi.org/10.1016/j.jaac.2012.02.019

Kasari, C., Paparella, T., Freeman, S., & Jahromi, L. B. (2008). Language outcome in autism: randomized comparison of joint attention and play interventions. *Journal of consulting and clinical psychology*, *76*(1), 125–137. https://doi.org/10.1037/0022-006X.76.1.125

Kim, J. E., Lyoo, I. K., Estes, A. M., Renshaw, P. F., Shaw, D. W., Friedman, S. D., Kim, D. J., Yoon, S. J., Hwang, J., & Dager, S. R. (2010). Laterobasal amygdalar enlargement in 6- to 7-year-old children with autism spectrum disorder. *Archives of general psychiatry*, *67*(11), 1187–1197. https://doi.org/10.1001/archgenpsychiatry.2010.148

Kirsch, P., Esslinger, C., Chen, Q., Mier, D., Lis, S., Siddhanti, S., Gruppe, H., Mattay, V. S., Gallhofer, B., & Meyer-Lindenberg, A. (2005). Oxytocin modulates neural circuitry for social cognition and fear in humans. *The Journal of neuroscience : the official journal of the Society for Neuroscience*, *25*(49), 11489–11493. https://doi.org/10.1523/JNEUROSCI.3984-05.2005

Klimek, L., Bergmann, K. C., Biedermann, T., Bousquet, J., Hellings, P., Jung, K., Merk, H., Olze, H., Schlenter, W., Stock, P., Ring, J., Wagenmann, M., Wehrmann, W., Mösges, R., & Pfaar, O. (2017). Visual analogue scales (VAS): Measuring instruments for the documentation of symptoms and therapy monitoring in cases of allergic rhinitis in everyday health care: Position Paper of the German Society of Allergology (AeDA) and the German Society of Allergy and Clinical Immunology (DGAKI), ENT Section, in collaboration with the working group on Clinical Immunology, Allergology and Environmental Medicine of the German Society of Otorhinolaryngology, Head and Neck Surgery (DGHNOKHC). *Allergo journal international*, *26*(1), 16–24. https://doi.org/10.1007/s40629-016-0006-7

Klintwall, L., Eldevik, S., & Eikeseth, S. (2015). Narrowing the gap: effects of intervention on developmental trajectories in autism. *Autism : the international journal of research and practice*, *19*(1), 53–63. https://doi.org/10.1177/1362361313510067

Koegel, L. K., Ashbaugh, K., & Koegel, R. L. (2016). Pivotal Response Treatment. In R. Lang, T. B. Hancock, & N. N. Singh (Eds.), *Early intervention for young children with autism spectrum disorder* (pp. 85–112). Springer International Publishing/Springer Nature. https://doi.org/10.1007/978-3-319-30925-5_4

Kohls, G., Schulte-Rüther, M., Nehrkorn, B., Müller, K., Fink, G. R., Kamp-Becker, I., Herpertz-Dahlmann, B., Schultz, R. T., & Konrad, K. (2013). Reward system dysfunction in autism spectrum disorders. *Social cognitive and affective neuroscience*, *8*(5), 565–572. https://doi.org/10.1093/scan/nss033

Kover, S. T., Edmunds, S. R., & Ellis Weismer, S. (2016). Brief Report: Ages of Language Milestones as Predictors of Developmental Trajectories in Young Children with Autism Spectrum Disorder. *Journal of autism and developmental disorders*, *46*(7), 2501–2507. https://doi.org/10.1007/s10803-016-2756-y

Kovshoff, H., Hastings, R. P., & Remington, B. (2011). Two-year outcomes for children with autism after the cessation of early intensive behavioral intervention. *Behavior modification*, *35*(5), 427–450. https://doi.org/10.1177/0145445511405513

Lai, M. C., Kassee, C., Besney, R., Bonato, S., Hull, L., Mandy, W., Szatmari, P., & Ameis, S. H. (2019). Prevalence of co-occurring mental health diagnoses in the autism population: a systematic review and meta-analysis. *The lancet. Psychiatry*, *6*(10), 819–829. https://doi.org/10.1016/S2215-0366(19)30289-5

Laister, D., Vivanti, G., Marschik, P. B., Fellinger, J., & Holzinger, D. (2021). Enhancement of Social Communication Behaviors in Young Children With Autism Affects Maternal Stress. *Frontiers in psychiatry*, *12*, 797148. https://doi.org/10.3389/fpsyt.2021.797148

Lamb, Y. N., Thompson, C. S., McKay, N. S., Waldie, K. E., & Kirk, I. J. (2015). The brain-derived neurotrophic factor (BDNF) val66met polymorphism differentially affects performance on subscales of the Wechsler Memory Scale - Third Edition (WMS-III). *Frontiers in psychology*, *6*, 1212. https://doi.org/10.3389/fpsyg.2015.01212

Landa R. J. (2018). Efficacy of early interventions for infants and young children with, and at risk for, autism spectrum disorders. *International review of psychiatry (Abingdon, England)*, *30*(1), 25–39. https://doi.org/10.1080/09540261.2018.1432574

Latrèche, K., Kojovic, N., Franchini, M., & Schaer, M. (2021). Attention to Face as a Predictor of Developmental Change and Treatment Outcome in Young Children with Autism Spectrum Disorder. *Biomedicines*, *9*(8), 942. https://doi.org/10.3390/biomedicines9080942

Law, M., Stewart, D., Pollock, N., Letts, L., Bosch, J., Westmorland, M. (1998). *Critical Review Form–Quantitative Studies*. McMaster University. [Retrieved from https://www.unisa.edu.au/siteassets/episerver-6-files/global/health/sansom/documents/icahe/cats/mcmasters_quantitative-review.pdf, accessed on March, 22, 2022]

Lena Research Foundation (2015). *User Guide LENA Pro*. Retrieved from: https://docplayer.net/44645642-User-guide-lena-pro-lena-research-foundation.html. Accessed on June 8th, 2022

Lewon, A.B., Ghezzi, P.M. (2021). An Evaluation of the Early Learning Measure as a Predictor of Outcomes in Early Intensive Behavioral Intervention. *Behavioral Interventions, 36,* 388–406. https://doi.org/10.1002/bin.1768

Lord, C., Bishop, S., & Anderson, D. (2015). Developmental trajectories as autism phenotypes. *American journal of medical genetics. Part C, Seminars in medical genetics*, *169*(2), 198–208. https://doi.org/10.1002/ajmg.c.31440

Lord, C., Luyster, R.J., Gotham, K., Guthrie, W. (2012). *Autism Diagnostic Observation Schedule, Second Edition (ADOS-2) Manual (Part II): Toddler Module*. Western Psychological Services

Lord, C., Rutter, M., & Le Couteur, A. (1994). Autism Diagnostic Interview-Revised: a revised version of a diagnostic interview for caregivers of individuals with possible pervasive developmental disorders. *Journal of autism and developmental disorders*, *24*(5), 659–685. https://doi.org/10.1007/BF02172145

Lord, C., Rutter, M., & Le Couteur, A. (1994). Autism Diagnostic Interview-Revised: a revised version of a diagnostic interview for caregivers of individuals with possible pervasive developmental disorders. *Journal of autism and developmental disorders, 24*(5), 659–685

Lotter, V. (1966). Epidemiology of Autistic Conditions in Young Children. *Social Psychiatry, 1*: 124–37.

Lovaas O. I. (1987). Behavioral treatment and normal educational and intellectual functioning in young autistic children. *Journal of consulting and clinical psychology*, *55*(1), 3–9. https://doi.org/10.1037//0022-006x.55.1.3

Lovaas, O.I. (1981). *Teaching Developmentally Disabled Children: The ME Book.* Pro-Ed

MacDonald, R., Parry-Cruwys, D., Dupere, S., & Ahearn, W. (2014). Assessing progress and outcome of early intensive behavioral intervention for toddlers with autism. *Research in developmental disabilities*, *35*(12), 3632–3644. https://doi.org/10.1016/j.ridd.2014.08.036

Magiati, I., Charman, T., & Howlin, P. (2007). A two-year prospective follow-up study of community-based early intensive behavioural intervention and specialist nursery provision for children with autism spectrum disorders. *Journal of child psychology and psychiatry, and allied disciplines*, *48*(8), 803–812. https://doi.org/10.1111/j.1469-7610.2007.01756.x

Magiati, I., Moss, J., Charman, T., & Howlin, P. (2011). Patterns of change in children with autism spectrum disorders who received community based comprehensive interventions in their pre-school years: A seven year follow-up study. *Research in Autism Spectrum Disorders*, *5*(3), 1016–1027. https://doi.org/10.1016/j.rasd.2010.11.007

Matson, J. L., & Kozlowski, A. M. (2011). The increasing prevalence of autism spectrum disorders. *Research in Autism Spectrum Disorders, 5*(1), 418-425. https://doi.org/10.1016/j.rasd.2010.06.004

McEachin, J. J., Smith, T., & Lovaas, O. I. (1993). Long-term outcome for children with autism who received early intensive behavioral treatment. *American Journal on Mental Retardation, 97*(4), 359–372

McIntosh, D. N., Miller, L. J., Shyu, V., & Dunn, W. (1999). Development and validation of the short sensory profile. *Sensory profile manual*, *61*, 59-73

Modabbernia, A., Velthorst, E., & Reichenberg, A. (2017). Environmental risk factors for autism: an evidence-based review of systematic reviews and meta-analyses. *Molecular autism*, *8*, 13. https://doi.org/10.1186/s13229-017-0121-4

Molnár, C., & Eldevik, S. (2017). Verhaltenstherapeutische Intervention für Vorschulkinder mit Autismus [Behavioral intervention for preschool children with autism – outcome of parent-based Intervention]. *Zeitschrift fur Kinder- und Jugendpsychiatrie und Psychotherapie*, *45*(3), 181–191. https://doi.org/10.1024/1422-4917/a000469

Mullen, E. (1995). *Mullen Scales of Early Learning* (AGS Edition). American Guidance Service

Ozonoff, S., & Iosif, A. M. (2019). Changing conceptualizations of regression: What prospective studies reveal about the onset of autism spectrum disorder. *Neuroscience and biobehavioral reviews*, *100*, 296–304. https://doi.org/10.1016/j.neubiorev.2019.03.012

Ozonoff, S., Young, G. S., Landa, R. J., Brian, J., Bryson, S., Charman, T., Chawarska, K., Macari, S. L., Messinger, D., Stone, W. L., Zwaigenbaum, L., & Iosif, A. M. (2015). Diagnostic stability in young children at risk for autism spectrum disorder: a baby siblings research consortium study. *Journal of child psychology and psychiatry, and allied disciplines*, *56*(9), 988–998. https://doi.org/10.1111/jcpp.12421

Pearson, N., Charman, T., Happé, F., Bolton, P. F., & McEwen, F. S. (2018). Regression in autism spectrum disorder: Reconciling findings from retrospective and prospective research. *Autism research : official journal of the International Society for Autism Research*, *11*(12), 1602–1620. https://doi.org/10.1002/aur.2035

Penzol, M. J., Salazar de Pablo, G., Llorente, C., Moreno, C., Hernández, P., Dorado, M. L., & Parellada, M. (2019). Functional Gastrointestinal Disease in Autism Spectrum Disorder: A Retrospective Descriptive Study in a Clinical Sample. *Frontiers in psychiatry*, *10*, 179. https://doi.org/10.3389/fpsyt.2019.00179

Perry, A., Cummings, A., Geier, J.D., Freeman, N.L., Hughes, S., Managhan, T., Reitzel, J.-A., Williams, J. (2011). Predictors of Outcome for Children Receiving Intensive Behavioral Intervention in a Large, Community-Based Program. *Research in Autism Spectrum Disorders*, *5*, 592–603. https://doi.org/10.1016/j.rasd.2010.07.003

Persico, A. M., Cucinotta, F., Ricciardello, A., Turriziani, L., & Chen, B. (2020). Chapter 3. Autisms. *Comprehensive Developmental Neuroscience. Neurodevelopmental Disorders*, 35-77. https://doi.org/10.1016/B978-0-12-814409-1.00003-3

Peters-Scheffer, N., Didden, R., Korzilius, H., & Sturmey, P. (2011). A meta-analytic study on the effectiveness of comprehensive ABA-based early intervention programs for children with Autism Spectrum Disorders. *Research in Autism Spectrum Disorders*, *5*(1), 60–69. https://doi.org/10.1016/j.rasd.2010.03.011

Pickles, A., Anderson, D. K., & Lord, C. (2014). Heterogeneity and plasticity in the development of language: a 17-year follow-up of children referred early for possible autism. *Journal of child psychology and psychiatry, and allied disciplines*, *55*(12), 1354–1362. https://doi.org/10.1111/jcpp.12269

R Core Team (2021). *R: A language and environment for statistical computing*. R Foundation for Statistical Computing, Vienna, Austria

R Core Team (2022). *R: A language and environment for statistical computing*. R Foundation for Statistical Computing, Vienna, Austria. URL: https://www.R-project.org/

Reilly, C., Atkinson, P., Das, K. B., Chin, R. F., Aylett, S. E., Burch, V., Gillberg, C., Scott, R. C., & Neville, B. G. (2014). Neurobehavioral comorbidities in children with active epilepsy: a population-based study. *Pediatrics*, *133*(6), e1586–e1593. https://doi.org/10.1542/peds.2013-3787

Remington, B., Hastings, R. P., Kovshoff, H., degli Espinosa, F., Jahr, E., Brown, T., Alsford, P., Lemaic, M., & Ward, N. (2007). Early intensive behavioral intervention: outcomes for children with autism and their parents after two years. *American journal of mental retardation : AJMR*, *112*(6), 418–438. https://doi.org/10.1352/0895-8017(2007)112[418:EIBIOF]2.0.CO;2

Reynell JK. (1990). *Reynell Developmental Language Scales*. Nfer-Nelson

Richler, J., Huerta, M., Bishop, S. L., & Lord, C. (2010). Developmental trajectories of restricted and repetitive behaviors and interests in children with autism spectrum disorders. *Development and psychopathology*, *22*(1), 55–69. https://doi.org/10.1017/S0954579409990265

Riva, V., Caruso, A., Apicella, F., Valeri, G., Vicari, S., Molteni, M., & Scattoni, M. L. (2021). Early developmental trajectories of expressive vocabulary and gesture production in a longitudinal cohort of Italian infants at high-risk for Autism Spectrum Disorder. *Autism research : official journal of the International Society for Autism Research*, *14*(7), 1421–1433. https://doi.org/10.1002/aur.2493

Rivard, M., Morin, M., Mello, C., Terroux, A., & Mercier, C. (2019). Follow-Up of Children With Autism Spectrum Disorder 1 Year After Early Behavioral Intervention. *Behavior modification*, *43*(4), 490–517. https://doi.org/10.1177/0145445518773692

Roane, H. S., Fisher, W. W., & Carr, J. E. (2016). Applied Behavior Analysis as Treatment for Autism Spectrum Disorder. *The Journal of pediatrics*, *175*, 27–32. https://doi.org/10.1016/j.jpeds.2016.04.023

Robain, F., Franchini, M., Kojovic, N., Wood de Wilde, H., & Schaer, M. (2020). Predictors of Treatment Outcome in Preschoolers with Autism Spectrum Disorder: An Observational Study in the Greater Geneva Area, Switzerland. *Journal of autism and developmental disorders*, *50*(11), 3815–3830. https://doi.org/10.1007/s10803-020-04430-6

Robain, F., Franchini, M., Kojovic, N., Wood de Wilde, H., & Schaer, M. (2020). Predictors of Treatment Outcome in Preschoolers with Autism Spectrum Disorder: An Observational Study in the Greater Geneva Area, Switzerland. *Journal of autism and developmental disorders*, *50*(11), 3815–3830. https://doi.org/10.1007/s10803-020-04430-6

Rogers, S. J., & Dawson, G. (2010a). *Early Start Denver Model curriculum checklist for young children with autism*. New York: Guilford Press

Rogers, S. J., Estes, A., Lord, C., Munson, J., Rocha, M., Winter, J., Greenson, J., Colombi, C., Dawson, G., Vismara, L. A., Sugar, C. A., Hellemann, G., Whelan, F., & Talbott, M. (2019). A Multisite Randomized Controlled Two-Phase Trial of the Early Start Denver Model Compared to Treatment as Usual. *Journal of the American Academy of Child and Adolescent Psychiatry*, *58*(9), 853–865. https://doi.org/10.1016/j.jaac.2019.01.004

Rogers, S. J., Lewis, H. C., & Reis, K. (1987). An Effective Procedure for Training Early Special Education Teams to Implement a Model Program. *Journal of the Division for Early Childhood*, *11*(2), 180–188. https://doi.org/10.1177/105381518701100210

Rogers, S. J., Stahmer, A., Talbott, M., Young, G., Fuller, E., Pellecchia, M., Barber, A., & Griffith, E. (2022). Feasibility of delivering parent-implemented NDBI interventions in low-resource regions: a pilot randomized controlled study. *Journal of neurodevelopmental disorders*, *14*(1), 3. https://doi.org/10.1186/s11689-021-09410-0

Rogers, S. J., Yoder, P., Estes, A., Warren, Z., McEachin, J., Munson, J., Rocha, M., Greenson, J., Wallace, L., Gardner, E., Dawson, G., Sugar, C. A., Hellemann, G., & Whelan, F. (2021). A Multisite Randomized Controlled Trial Comparing the Effects of Intervention Intensity and Intervention Style on Outcomes for Young Children With Autism. *Journal of the American Academy of Child and Adolescent Psychiatry*, *60*(6), 710–722. https://doi.org/10.1016/j.jaac.2020.06.013

Rogers, S.J., Dawson, G. (2010b). *Early Start Denver Model for Young Children with Autism: Promoting language, learning, and engagement.* New York: Guilford Press

Rogers, S.J., Vivanti, G., Rocha, M. (2017). *Helping Young Children with Autism Spectrum Disorder Develop Social Ability: The Early Start Denver Model Approach*. In: Leaf, J. (eds) Handbook of Social Skills and Autism Spectrum Disorder. Autism and Child Psychopathology Series. Springer, Cham. https://doi.org/10.1007/978-3-319-62995-7_13

Rosen, N. E., Lord, C., & Volkmar, F. R. (2021). The Diagnosis of Autism: From Kanner to DSM-III to DSM-5 and Beyond. Journal of autism and developmental disorders, 51(12), 4253–4270. https://doi.org/10.1007/s10803-021-04904-1

Russell, G., Mandy, W., Elliott, D., White, R., Pittwood, T., & Ford, T. (2019). Selection bias on intellectual ability in autism research: a cross-sectional review and meta-analysis. *Molecular autism*, *10*, 9. https://doi.org/10.1186/s13229-019-0260-x

Sallows, G. O., & Graupner, T. D. (2005). Intensive behavioral treatment for children with autism: four-year outcome and predictors. *American journal of mental retardation: AJMR*, *110*(6), 417–438. https://doi.org/10.1352/0895-8017(2005)110[417:IBTFCW]2.0.CO;2

Sallows, G. O., & Graupner, T. D. (2005). Intensive behavioral treatment for children with autism: four-year outcome and predictors. *American journal of mental retardation : AJMR*, *110*(6), 417–438. https://doi.org/10.1352/0895-8017(2005)110[417:IBTFCW]2.0.CO;2

Schaefer, G. B., Mendelsohn, N. J., & Professional Practice and Guidelines Committee (2013). Clinical genetics evaluation in identifying the etiology of autism spectrum disorders: 2013 guideline revisions. *Genetics in medicine : official journal of the American College of Medical Genetics*, *15*(5), 399–407. https://doi.org/10.1038/gim.2013.32

Schopler, E., Lansing, M. D., Reichler, R. J., & Marcus, L. M. (2005). *Psychoeducational profile: TEACCH individualized psychoeducational assessment for children with autism spectrum disorders (PEP-3) 3*. Pro-Ed

Schopler, E., Lansing, M.D., Reichler, R.J., Marcus, L.M. (2005). *Psychoeducational Profile: TEACCH Individualized Psychoeducational Assessment for Children with Autism Spectrum Disorders* (3rd ed.). Pro-Ed

Schopler, E., Reichler, R.J., Renner, B.R. (2002). *The Childhood Autism Rating Scale (CARS).* Western Psychological Services

Schreibman, L., Dawson, G., Stahmer, A. C., Landa, R., Rogers, S. J., McGee, G. G., Kasari, C., Ingersoll, B., Kaiser, A. P., Bruinsma, Y., McNerney, E., Wetherby, A., & Halladay, A. (2015). Naturalistic Developmental Behavioral Interventions: Empirically Validated Treatments for Autism Spectrum Disorder. *Journal of autism and developmental disorders*, *45*(8), 2411–2428. https://doi.org/10.1007/s10803-015-2407-8

Schreibman, L., Stahmer, A. C., Barlett, V. C., & Dufek, S. (2009). Brief Report: Toward Refinement of a Predictive Behavioral Profile for Treatment Outcome in Children with Autism. *Research in autism spectrum disorders*, *3*(1), 163–172. https://doi.org/10.1016/j.rasd.2008.04.008

Sheinkopf, S. J., & Siegel, B. (1998). Home-based behavioral treatment of young children with autism. *Journal of autism and developmental disorders*, *28*(1), 15–23. https://doi.org/10.1023/a:1026054701472

Sherer, M. R., & Schreibman, L. (2005). Individual behavioral profiles and predictors of treatment effectiveness for children with autism. *Journal of consulting and clinical psychology*, *73*(3), 525–538. https://doi.org/10.1037/0022-006X.73.3.525

Sikich, L., Kolevzon, A., King, B. H., McDougle, C. J., Sanders, K. B., Kim, S. J., Spanos, M., Chandrasekhar, T., Trelles, M. D. P., Rockhill, C. M., Palumbo, M. L., Witters Cundiff, A., Montgomery, A., Siper, P.,

Minjarez, M., Nowinski, L. A., Marler, S., Shuffrey, L. C., Alderman, C., Weissman, J., Zappone, B., Mullet, J. E., Crosson, H., Hong, N., Siecinksi, S. K., Giambernardino, S. N., Luo, S., She, L., Bhapkar, M., Dean, R., Scheer, A., Johnson, J. L., Gregory, S. G., and Veenstra-VanderWeele, J. (2021). Intranasal Oxytocin in Children and Adolescents with Autism Spectrum Disorder. *The New England journal of medicine*, *385*(16), 1462–1473. https://doi.org/10.1056/NEJMoa2103583

Siller, M., Swanson, M., Gerber, A., Hutman, T., & Sigman, M. (2014). A parent-mediated intervention that targets responsive parental behaviors increases attachment behaviors in children with ASD: results from a randomized clinical trial. *Journal of autism and developmental disorders*, *44*(7), 1720–1732. https://doi.org/10.1007/s10803-014-2049-2

Sinai-Gavrilov, Y., Gev, T., Mor-Snir, I., Vivanti, G., & Golan, O. (2020). Integrating the Early Start Denver Model into Israeli community autism spectrum disorder preschools: Effectiveness and treatment response predictors. *Autism : the international journal of research and practice*, *24*(8), 2081–2093. https://doi.org/10.1177/1362361320934221

Smith, D. P., Hayward, D. W., Gale, C. M., Eikeseth, S., & Klintwall, L. (2021). Treatment Gains from Early and Intensive Behavioral Intervention (EIBI) are Maintained 10 Years Later. *Behavior modification*, *45*(4), 581–601. https://doi.org/10.1177/0145445519882895

Smith, T., Groen, A. D., & Wynn, J. W. (2000). Randomized trial of intensive early intervention for children with pervasive developmental disorder. *American journal of mental retardation : AJMR*, *105*(4), 269–285. https://doi.org/10.1352/0895-8017(2000)105<0269:RTOIEI>2.0.CO;2

Smith, T., Klorman, R., & Mruzek, D. W. (2015). Predicting Outcome of Community-Based Early Intensive Behavioral Intervention for Children with Autism. *Journal of abnormal child psychology*, *43*(7), 1271–1282. https://doi.org/10.1007/s10802-015-0002-2

Sparrow, S.S., Cicchetti, D.V., Saulnier, C.A. (2016). *Vineland Adaptive Behavior Scales* (3rd ed.). Psychological Corporation

Sparrow, S.S.; Bella, D.A.; Cicchetti, D.V. (1984). *The Vineland Adaptive Behavior Scale*. American Guidance Service

Sparrow, S.S.; Cicchetti, D.V.; Bella, D.A. (2005). *Vineland-II Adaptive Behavior Scales* (2nd edition). NCS Pearson

Stanfield, A. C., McIntosh, A. M., Spencer, M. D., Philip, R., Gaur, S., & Lawrie, S. M. (2008). Towards a neuroanatomy of autism: a systematic review and meta-analysis of structural magnetic resonance imaging studies. *European psychiatry : the journal of the Association of European Psychiatrists*, *23*(4), 289–299. https://doi.org/10.1016/j.eurpsy.2007.05.006

Strauss, K., Vicari, S., Valeri, G., D'Elia, L., Arima, S., & Fava, L. (2012). Parent inclusion in Early Intensive Behavioral Intervention: the influence of parental stress, parent treatment fidelity and parent-mediated generalization of behavior targets on child outcomes. *Research in developmental disabilities*, *33*(2), 688–703. https://doi.org/10.1016/j.ridd.2011.11.008

Stutsman, R. (1948). *Guide for Administering the Merrill-Palmer Scale of Mental Tests.* Harcourt, Brace & World

Sulek, R., Smith, J., Bent, C. A., Hudry, K., Trembath, D., Vivanti, G., & Dissanayake, C. (2022). The utility of LENA as an indicator of developmental outcomes for young children with autism. *International journal of language & communication disorders*, *57*(1), 103–111. https://doi.org/10.1111/1460-6984.12678

Thorndike, R.L. (1972). *Manual for Stanford-Binet Intelligence Scale*. Houghton Mifflin

Thorndike, R.L. (1986). Stanford-Binet Intelligence Scale (4th ed)

Thurm, A., Farmer, C., Salzman, E., Lord, C., & Bishop, S. (2019). State of the Field: Differentiating Intellectual Disability From Autism Spectrum Disorder. *Frontiers in psychiatry*, *10*, 526. https://doi.org/10.3389/fpsyt.2019.00526

Tick, B., Bolton, P., Happé, F., Rutter, M., & Rijsdijk, F. (2016). Heritability of autism spectrum disorders: a meta-analysis of twin studies. *Journal of child psychology and psychiatry, and allied disciplines*, *57*(5), 585–595. https://doi.org/10.1111/jcpp.12499

Tiede, G., & Walton, K. M. (2019). Meta-analysis of naturalistic developmental behavioral interventions for young children with autism spectrum disorder. *Autism: the international journal of research and practice*, *23*(8), 2080–2095. https://doi.org/10.1177/1362361319836371

Tolles, J., & Meurer, W. J. (2016). Logistic Regression: Relating Patient Characteristics to Outcomes. *JAMA*, *316*(5), 533–534. https://doi.org/10.1001/jama.2016.7653

Ventola, P., Yang, D. Y., Friedman, H. E., Oosting, D., Wolf, J., Sukhodolsky, D. G., & Pelphrey, K. A. (2015). Heterogeneity of neural mechanisms of response to pivotal response treatment. *Brain imaging and behavior*, *9*(1), 74–88. https://doi.org/10.1007/s11682-014-9331-y

Virués-Ortega J. (2010). Applied behavior analytic intervention for autism in early childhood: meta-analysis, meta-regression and dose-response meta-analysis of multiple outcomes. *Clinical psychology review*, *30*(4), 387–399. https://doi.org/10.1016/j.cpr.2010.01.008

Virués-Ortega, J., Julio, F. M., & Pastor-Barriuso, R. (2013). The TEACCH program for children and adults with autism: a meta-analysis of intervention studies. *Clinical psychology review*, *33*(8), 940–953. https://doi.org/10.1016/j.cpr.2013.07.005

Virues-Ortega, J., Rodríguez, V., & Yu, C. T. (2013). Prediction of treatment outcomes and longitudinal analysis in children with autism undergoing intensive behavioral intervention. *International Journal of Clinical and Health Psychology*, *13*(2), 91-100. https://doi.org/10.1016/S1697-2600(13)70012-7

Vivanti, G., Dissanayake, C., & Victorian ASELCC Team (2016). Outcome for Children Receiving the Early Start Denver Model Before and After 48 Months. *Journal of autism and developmental disorders*, *46*(7), 2441–2449. https://doi.org/10.1007/s10803-016-2777-6

Vivanti, G., Dissanayake, C., Duncan, E., Feary, J., Capes, K., Upson, S., Bent, C. A., Rogers, S. J., Hudry, K., & Victorian ASELCC Team (2019). Outcomes of children receiving Group-Early Start Denver Model in an inclusive versus autism-specific setting: A pilot randomized controlled trial. *Autism : the international journal of research and practice*, *23*(5), 1165–1175. https://doi.org/10.1177/1362361318801341

Vivanti, G., Dissanayake, C., Zierhut, C., Rogers, S. J., & Victorian ASELCC Team (2013). Brief report: Predictors of outcomes in the Early Start Denver Model delivered in a group setting. *Journal of autism and developmental disorders*, *43*(7), 1717–1724. https://doi.org/10.1007/s10803-012-1705-7

Vivanti, G., Prior, M., Williams, K., & Dissanayake, C. (2014*a*). Predictors of outcomes in autism early intervention: why don't we know more?. *Frontiers in pediatrics*, *2*, 58. https://doi.org/10.3389/fped.2014.00058

Vivanti, G., Paynter, J., Duncan, E., Fothergill, H., Dissanayake, C., Rogers, S. J., & Victorian ASELCC Team (2014*b*). Effectiveness and feasibility of the early start denver model implemented in a group-based community childcare setting. *Journal of autism and developmental disorders*, *44*(12), 3140–3153. https://doi.org/10.1007/s10803-014-2168-9

Vivanti, G., Zhong, H.N. (2020). Naturalistic Developmental Behavioral Interventions for Children with Autism. In: Vivanti, G., Bottema-Beutel, K., Turner-Brown, L. (eds) Clinical Guide to Early Interventions for Children with Autism. Best Practices in Child and Adolescent Behavioral Health Care. Springer, Cham. https://doi.org/10.1007/978-3-030-41160-2_6

Vorstman, J. A., Spooren, W., Persico, A. M., Collier, D. A., Aigner, S., Jagasia, R., Glennon, J. C., & Buitelaar, J. K. (2014). Using genetic findings in autism for the development of new pharmaceutical compounds. *Psychopharmacology*, *231*(6), 1063–1078. https://doi.org/10.1007/s00213-013-3334-z

Waddington, H., van der Meer, L., & Sigafoos, J. (2016). Effectiveness of the Early Start Denver Model: a systematic review. *Review Journal of Autism and Developmental Disorders*, *3*(2), 93-106. https://doi.org/10.1007/s40489-015-0068-3

Wang, S. H., Zhang, H. T., Zou, Y. Y., Cheng, S. M., Zou, X. B., & Chen, K. Y. (2022). Efficacy and moderating factors of the Early Start Denver Model in Chinese toddlers with autism spectrum disorder: a longitudinal study. *World journal of pediatrics : WJP*, 10.1007/s12519-022-00555-z. Advance online publication. https://doi.org/10.1007/s12519-022-00555-z

Wechsler, D. (1974). *Manual for the Wechsler Intelligence Scale for Children-Revised* (Revised edition). Psychological Corporation.

Wechsler, D. (1989). *WPPSI-R: Wechsler Preschool and Primary Scale of Intelligence-Revised* (Revised edition). Psychological Corporation.

Wechsler, D. (2008). *Wechsler Preschool and Primary Scale of Intelligence: WPPSI III* (3rd ed.). Giunti O.S.

Weiss, M. J. (1999). Differential rates of skill acquisition and outcomes of early intensive behavioral intervention for autism. *Behavioral Interventions*, *14*(1), 3–22. https://doi.org/10.1002/(SICI)1099-078X(199901/03)14:1<3::AID-BIN25>3.0.CO;2-F

Wong, C., Odom, S. L., Hume, K. A., Cox, A. W., Fettig, A., Kucharczyk, S., Brock, M. E., Plavnick, J. B., Fleury, V. P., & Schultz, T. R. (2015). Evidence-Based Practices for Children, Youth, and Young Adults with Autism Spectrum Disorder: A Comprehensive Review. *Journal of autism and developmental disorders*, *45*(7), 1951–1966. https://doi.org/10.1007/s10803-014-2351-z

World Health Organization. (1993). *The ICD-10 classification of mental and behavioural disorders: Diagnostic criteria for research*

Wulffaert, J., Van Berckelaer-Onnes, I. A., & Scholte, E. M. (2009). Autistic disorder symptoms in Rett syndrome. *Autism: the international journal of research and practice*, *13*(6), 567–581. https://doi.org/10.1177/1362361309338184

Yoo, H. (2016). Early detection and intervention of autism spectrum disorder. *Hanyang Medical Reviews*, *36*(1), 4-10. https://doi.org/10.7599/hmr.2016.36.1.4

Zachor, D. A., & Itzchak, E. B. (2010). Treatment approach, autism severity and intervention outcomes in young children. *Research in Autism Spectrum Disorders*, *4*(3), 425-432

Zachor, D. A., Ben-Itzchak, E., Rabinovich, A. L., & Lahat, E. (2007). Change in autism core symptoms with intervention. *Research in autism spectrum disorders*, *1*(4), 304-317. https://doi.org/10.1016/j.rasd.2006.12.001

Zachor, D. A., Ben-Itzchak, E., Rabinovich, A. L., & Lahat, E. (2007). Change in autism core symptoms with intervention. *Research in autism spectrum disorders*, *1*(4), 304-317. https://doi.org/10.1016/j.rasd.2006.12.001

Zeidan, J., Fombonne, E., Scorah, J., Ibrahim, A., Durkin, M. S., Saxena, S., Yusuf, A., Shih, A., & Elsabbagh, M. (2022). Global prevalence of autism: A systematic review update. *Autism research : official journal of the International Society for Autism Research, 15(5)*, 778–790. https://doi.org/10.1002/aur.2696

Zitter, A., Rinn, H., Szapuova, Z., Avila-Pons, V. M., Coulter, K. L., Stahmer, A. C., Robins, D. L., & Vivanti, G. (2021). Does Treatment Fidelity of the Early Start Denver Model Impact Skill Acquisition in Young Children with Autism?. *Journal of autism and developmental disorders*, 10.1007/s10803-021-05371-4. Advance online publication. https://doi.org/10.1007/s10803-021-05371-4

Zwaigenbaum, L., Bauman, M. L., Choueiri, R., Kasari, C., Carter, A., Granpeesheh, D., Mailloux, Z., Smith Roley, S., Wagner, S., Fein, D., Pierce, K., Buie, T., Davis, P. A., Newschaffer, C., Robins, D., Wetherby, A., Stone, W. L., Yirmiya, N., Estes, A., Hansen, R. L., … Natowicz, M. R. (2015*a*). Early Intervention for Children With Autism Spectrum Disorder Under 3 Years of Age: Recommendations for Practice and Research. *Pediatrics, 136 Suppl 1*, S60–S81. https://doi.org/10.1542/peds.2014-3667E

Zwaigenbaum, L., Bauman, M. L., Fein, D., Pierce, K., Buie, T., Davis, P. A., Newschaffer, C., Robins, D. L., Wetherby, A., Choueiri, R., Kasari, C., Stone, W. L., Yirmiya, N., Estes, A., Hansen, R. L., McPartland, J. C., Natowicz, M. R., Carter, A., Granpeesheh, D., Mailloux, Z., … Wagner, S. (2015*b*). Early Screening of Autism Spectrum Disorder: Recommendations for Practice and Research. *Pediatrics, 136 Suppl 1*, S41–S59. https://doi.org/10.1542/peds.2014-3667D

Zwaigenbaum, L., Bauman, M. L., Stone, W. L., Yirmiya, N., Estes, A., Hansen, R. L., McPartland, J. C., Natowicz, M. R., Choueiri, R., Fein, D., Kasari, C., Pierce, K., Buie, T., Carter, A., Davis, P. A., Granpeesheh, D., Mailloux, Z., Newschaffer, C., Robins, D., Roley, S. S., … Wetherby, A. (2015*c*). Early Identification of Autism Spectrum Disorder: Recommendations for Practice and Research. *Pediatrics, 136 Suppl 1*, S10–S40. https://doi.org/10.1542/peds.2014-3667C

Zwaigenbaum, L., Brian, J. A., & Ip, A. (2019). Early detection for autism spectrum disorder in young children. *Paediatrics & child health*, *24*(7), 424–443. https://doi.org/10.1093/pch/pxz119

Supplementary Materials

Table S1. Summary of EIBI studies excluded from our systematic review due to a patient recruitment age range beyond 48 months: sample characteristics.

Study	Cases				Controls			
	N (M:F)	Age at intake in months (mean)	Diagnosis	Exclusion criteria	Control Intervention	N (M:F)	Age at intake in months (mean)	Diagnosis
Dimian et al., 2021	667 (548:119)	24-72 (mean age n.r)	n.r.	n.r.	---	---	---	---
Eikeseth et al., 2002/2007	13 (7:5)	48-84 (66)	ICD-10 ADI-R	• IQ > 50. • Age at intake < 48 and > 84. • Severe medical conditions.	Eclectic	12 (11:1)	48-84 (65)	ASD
Eikeseth et al., 2012	35 (29:6)	25-76 (47)	ICD-10	Authors report excluding one child because she was re-diagnosed with Rett's syndrome diagnosis.	TAU	24 (20:4)	24-88 (53)	ASD
Eldevik et al., 2006	13 (10:3)	36-68 (53)	ICD-10 ADI-R	• Severe medical conditions. • CA > 72 at treatment start.	Eclectic	15 (14:1)	21-69 (49)	ASD

Study	Cases				Controls			
	N (M:F)	Age at intake in months (mean)	Diagnosis	Exclusion criteria	Control Intervention	N (M:F)	Age at intake in months (mean)	Diagnosis
Eriksson et al., 2013	93 (gender n.r.)	20-54 (38)	DSM-IV	• "Complex" cases with ASD. • No exclusion of children with medical/genetic/neurological conditions or ID.	Less-intensive ABA	105 (gender n.r.)	20-54 (43.5)	ASD
Flanagan et al., 2012	79 (gender n.r.)	range n.r. (43)	CARS	No exclusion criteria based on comorbid diagnosis or skills level.	None (Waitlist for IBI)	63 (gender n.r.)	range n.r. (43)	ASD
Frazier et al., 2021	131 (114:17)	17-71 (40)	DSM ADOS CARS	Not based on symptoms, cognitive or functional severity.	---	---	---	---
Goin-Kochel et al., 2007	29 (27:2)	30-61 (46)	ADI-R ADOS	Not being registered in the school where EIBI was delivered.	---	---	---	---
Granpeesheh et al., 2009	245 (gender n.r.)	16-144 (73)	n.r.	• Age at intake < 16 or > 144 months. • Being in treatment for < 1 or > 48 months.	---	---	---	---
Harris & Handleman, 2000	27 (23:4)	31-65 (49)	DSM-III CARS	n.r.	---	---	---	---
Klintwall & Eikeseth, 2012	21 (16:5)	27-59 (43)	CARS	Authors report excluding one child because she was re-diagnosed with Rett's syndrome diagnosis.	---	---	---	---

Study	Cases				Controls			
	N (M:F)	Age at intake in months (mean)	Diagnosis	Exclusion criteria	Control Intervention	N (M:F)	Age at intake in months (mean)	Diagnosis
Lewon & Ghezzi 2021	13 (13:0)	28-56	DSM-IV GARS-2	Comorbid psychiatric disorder.	---	---	---	---
Luiselli et al., 2000	16 (15:1)	26-57 (m=32 for children aged < 36 mo.; m=48 for children aged > 36 mo.)	Clinical diagnosis independent of the study	n.r.	---	---	---	---
Magiati et al., 2007; 2011	28 (27:1)	22-54 (38)	Clinical diagnosis independent of the study ADI-R	Severe medical conditions.	TAU	16 (12:4)	22-54 (42.5)	ASD
Perry et al., 2011	332 (276:56)	20-86 (54)	DSM-IV CARS	No exclusion criteria based on neurological/genetic conditions.	---	---	---	---
Préfontaine et al., 2022	233 (184:49)	24-69 (52)	Clinical diagnosis independent of the study CARS-2	Age beyond 60 months at intake.	---	---	---	---
Rivard et al., 2019	32 (21:11)	37-59	GARS-2 CARS	n.r.	---	---	---	---

Study	Cases				Controls			
	N (M:F)	Age at intake in months (mean)	Diagnosis	Exclusion criteria	Control Intervention	N (M:F)	Age at intake in months (mean)	Diagnosis
Smith et al., 2015	71 (60:11)	24-59 (39)	ADOS ADI-R	Severe medical/genetic conditions.	---	---	---	---
Stoelb et al., 2004	19 (14:5)	26-122 (56)	DSM-IV CARS	n.r.	---	---	---	---
Virués-Ortega et al., 2013	24 (21:3)	range n.r. (50)	DSM-IV-R ADOS-2 ADI-R	No exclusion based on children functioning.	---	---	---	---
Waters et al., 2018	48 (45:3)	18-75 (38)	Clinical diagnosis independent of the study ADI-R	• Severe medical conditions. • IQ>35.	TAU	46 (45:1)	18-75 (42)	ASD
Weiss, 1999	20 (19:1)	20-65 (41.5)	DSM-IV CARS	n.r.	---	---	---	---

ADI-R: Autism Diagnostic Interview-Revised; ADOS: Autism Diagnostic Observation Schedule; ASD: Autism Spectrum Disorder; CARS: Childhood Autism Rating Scale; DSM: Diagnostic and Statistical Manual of Mental Disorders; ESDM: Early Start Denver Model; GARS: Gilliam Autism Rating Scale; IBI: Intensive Behavioral Intervention; ICD: International Classification of Diseases; n.r.: Not Reported; P-EIBI: Parent-delivered Early Intensive Behavioral Intervention; TAU: Treatment as Usual.

Table S2. Summary of EIBI studies excluded from our systematic review due to a patient recruitment age range beyond 48 months: interventions characteristics.

Study	Country	Study design	Intervention type	Setting	Intensity	Duration
Dimian et al., 2021	USA	Retrospective population-based observational study	EIBI	n.r.	19 hrs/wk	24 months
Eikeseth et al., 2002/2007	Norway	Case-control trial/Follow-up	UCLA EIBI	School based	28 hrs/wk	12 mo
Eikeseth et al., 2012	Sweden	Comparison-controlled trial	UCLA EIBI	Preschool/Kindergarten	15-37 hrs/wk	12 mo
Eldevik et al., 2006	Norway	Retrospective study	UCLA EIBI	Kindergarten/Elementary school	12,5 hrs/wk	20 mo
Eriksson et al., 2013	Sweden	Prospective population-based two-year follow-up study	EIBI	• Home-based • Kindergarten (see Fernell et al. 2011)	15-40 hrs/wk	24 mo
Flanagan et al., 2012	Canada	Retrospective study	IBI	• Community-based • Home-based (occasionally)	26 hrs/wk	24 mo

Study	Country	Study design	Intervention type	Setting	Intensity	Duration
Frazier et al., 2021	USA	Retrospective study	EIBI	School based	30 hrs/wk	2-49 (m=24) mo
Goin-Kochel et al., 2007	USA	Retrospective study	EIBI	Special ASD kindergarten	30 hrs/wk	2-28 (m=11) mo
Granpeesheh et al., 2009	USA	Retrospective study	ABA	Community-based	20-168 (m=78)	n.r.
Harris & Handleman, 2000	USA	One group pretest-posttest design	ABA	University center-based preschool program	35-45 hrs/wk	12 mo
Klintwall and Eikeseth, 2012	Sweden	One group pretest-posttest design	UCLA EIBI	• Home-based • Kindergarten	20 hrs/wk	12 mo
Lewon and Ghezzi 2021	USA	Retrospective study	EIBI	n.r.	15-38 (m=30) hrs/wk	39 mo
Luiselli et al., 2000	USA	Retrospective study	UCLA EIBI	Home-based	12-15 hrs/wk	7-11 mo
Magiati et al., 2007; 2011	UK	Case-control trial/Follow-up	UCLA EIBI	Home-based	32 hrs/wk	24 mo
Perry et al., 2011	Canada	Retrospective study	IBI	• Home-based • Center-based • Childcare setting	20-40 hrs/wk	4-47 (m=18) mo

Study	Country	Study design	Intervention type	Setting	Intensity	Duration
Préfontaine et al., 2022	Canada	Prospective longitudinal study	EIBI	Community-based	4-12 hrs/wk (low intensity) or 16-20 hrs/week (moderate intensity)	12 mo
Rivard et al., 2019	Canada	One group pretest-posttest design/1-year follow-up	UCLA EIBI	n.r.	10-20 (m=15) hrs/wk	12 mo
Smith et al., 2015	USA	One group pretest-posttest design	UCLA EIBI	Community-based	15 hours/week for 12 months	12 mo
Stoelb et al., 2004	USA	Retrospective study	UCLA EIBI	Home/School/Daycare setting	12-36 hours/week for 12 months	12 mo
Virués-Ortega et al., 2013	Spain	One group pretest-posttest design	UCLA EIBI	Home-based	15-47 (m=31) hrs/wk	5-59 (m=22) mo
Waters et al., 2018	USA	Case-control trial	UCLA EIBI	n.r.	35-40 hrs/wk	36 mo
Weiss, 1999	USA	Retrospective study	EIBI	Home-based	40 hrs/wk	24 mo

ABA: Applied Behavioral Analysis; EIBI: Early Intensive Behavioral Intervention; IBI: Intensive Behavioral Intervention; IQ: Intellectual Quotient; MA: Mental Age; n.r.: not reported; RCT: Randomized Controlled Trial; UCLA: University of California: Los Angeles.

Table S3. Summary of EIBI predictors of positive outcome in studies excluded due to a patient recruitment age range beyond 48 months.

Study	Predictors of better outcome	Improved functions correlated with predictors	Non-predictors
Dimian et al., 2021	• Younger age at intake. • Higher IQ.	• Higher odds of being enrolled in regular (vs. special) classes. • Lower probability of needing special education services at school.	None reported
Eikeseth et al., 2002/2007	• Higher intake IQ	• Higher post-treatment IQ and language skills and changes in language (but not IQ) scores. • Higher 3-year-follow-up IQ and adaptive behaviors (VABS, except for Social domain).	Age at intake
Eikeseth et al., 2012	• None found		• Age at intake. • Adaptive behaviors. • Maladaptive behaviors. • Autism severity symptoms.
Eldevik et al., 2006	• Higher intake IQ. • Higher language skills at intake.	• Post-treatment IQ. • Adaptive behaviors. • Non-verbal IQ. • Language skills.	• Age at intake. • Non-verbal IQ. • Adaptive behaviors
Eriksson et al., 2013	• Not having a medical/genetic condition (including epilepsy). • No history of regression. • Older age at intake.	• Adaptive behaviors (VABS).	• None reported.
Flanagan et al., 2012	• Younger age at intake. • Adaptive behaviors.*	• Post-treatment IQ.	• Autism severity symptoms.

Study	Predictors of better outcome	Improved functions correlated with predictors	Non-predictors
Frazier et al., 2021	• Younger age at intake. • Lower autistic symptoms severity. • Higher verbal and non-verbal cognitive functions.	• Post-treatment language skills.	• None reported.
Goin-Kochel et al., 2007	• Overall pre-treatment functioning. • Responsiveness to treatment within the first 6 months. • Younger age at intake.	• Overall post-treatment functioning. • Improved adaptive behaviors.	• None reported.
Granpeesheh et al., 2009	• Younger age at intake.	• Number of monthly mastered behavioral objectives.	• None reported.
Harris & Handleman, 2000	• Younger age at intake. • Higher IQ at intake.	• Higher odds of being enrolled in regular (vs. special) education class.	• Autism severity symptoms
Klintwall and Eikeseth, 2012	• Older age at intake. • Number of socially mediated (vs. automatic) stimuli that functioned as reinforcers.	• Better learning rate.	• Adaptive behaviors
Lewon and Ghezzi 2021	• 3-months improvement in expressive language skills and receptive language skills.	• Improved adaptive behaviors. • • Improved severity symptoms (except for stereotyped behaviors).	• Age at intake. • Adaptive behaviors. • Autism symptoms severity. • Non-verbal imitation
Luiselli et al., 2000	• None found (except for treatment intensity).	•	• Age at intake.

Study	Predictors of better outcome	Improved functions correlated with predictors	Non-predictors
Magiati et al., 2007; 2011	• Higher IQ at intake. • Receptive language. • Adaptive behaviors. • Autism symptoms severity.	• Better overall post-treatment gains. • Except for severity symptoms, these variables predicted treatment outcome at 5-years follow-up.	• Age at intake.
Perry et al., 2011	• Higher IQ at intake. • Younger age at intake. • Higher adaptive behaviors at intake. • Autism symptoms severity at intake.	• Post-treatment adaptive behaviors. • Post-treatment IQ. • Post-treatment smptoms severity.	• None reported.
Préfontaine et al., 2022	• Level of pre-treatment impairment profile.	• Children with pre-treatment moderate to severe impairment profile continued to progress overall one year after the end of EIBI in conceptual and social domain, while children with pre-treatment mild impairment profile continued to progress in practical domain.	• None reported.
Rivard et al., 2019	• Higher IQ at intake. • Autism severity symptoms at intake.	• 1-year follow-up IQ and adaptive behaviors. • 1-year follow-up severity symptoms.	• Adaptive behaviors.
Smith et al., 2015	• Higher pre-treatment functioning. • Younger age at intake. • MSEL DQ at intake. • Social engagement.	• Overall better post-treatment and 1-year follow-upfunction. • Improved post-treatment and 1-year follow-up DQ and adaptive behavior. • Improved post-treatment symptoms severity.	• Sensory-motor rituals.

Study	Predictors of better outcome	Improved functions correlated with predictors	Non-predictors
Stoelb et al., 2004	• Having no dysmorphic physical features nor history of regression. • Older age at intake.	• Better outcome at 6 and 12 months. • Better post-treatment language skills.	• Overall pretreatment functioning. • MRI results. • Head circumference. • History of seizures. • Sleep problems. • Gender. • "Complex"** autism
Virués-Ortega et al., 2013	• Younger age at intake. • Pre-intervention functioning.	• Gross motor skills, receptive language, self-care skills and social behaviors. • Fine motor skills, prewriting skills, cognitive abilities and expressive language.	• None reported
Waters et al., 2018	• Younger age was at treatment start.	• Non-verbal IQ/DQ. • Adaptive behaviors.	• None reported
Weiss, 1999	• Rate of learning.	• Improved adaptive behaviors and symptoms severity.	• None reported

* Analysis performed on a subgroup of children: n=61 from intervention group vs. n=61 from comparison group.
**All participants who exhibited abnormal MRI results, microcephaly or physical dysmorphology were classified as complex autism cases.
ABLLS: Assessment of Basic Language and Learning Skills; ADI-R: Autism Diagnostic Interview-Revised; ADOS: Autism Diagnostic Observation Schedule; DQ: Developmental Quotient; EIBI: Early Intensive Behavioral Intervention; GARS: Gilliam Autism Rating Scale; IQ: Intellectual Quotient; MSEL: Mullen Scales of Early Learning; TAU: Treatment as Usual; VABS: Vineland Adaptive Behavior Scale

Table 4. Summary of ESDM studies excluded from our systematic review due to a patient recruitment age range beyond 48 months: sample characteristics.

Study	Cases				Controls			
	N (M:F)	Age at intake in months (mean)	Diagnosis	Excluding criteria	Control Intervention	N (M:F)	Age at intake in months (mean)	Diagnosis
Fulton et al., 2014	38 (35:3)	39-64 (52)	DSM-IV-TR	• Neurological disorders. • Significant hearing, vision, motor, or physical impairments.	---	---	---	---
Geoffrey et al., 2019	19 (15:4)	22-50 (35)	DSM-5 ADOS-2	• Severe medical conditions.	---	---	---	---
Laister et al., 2021	56 (51:5)	29-60 (42)	DSM-IV ADOS-2	• Nonverbal DA < 12 months. • Diagnosis > 48 months of age.	---	---	---	---
Robain et al., 2020	22 (22:0)	20-60 (31)	DSM-5 ADOS-2	• Neurodevelopmental disorders of known genetic etiology. • Severe medical condition.	CT	38 (38:0)	20-60 (40)	ASD
Sinai-Gavrilov et al., 2020	26 (20:6)	33-57 (44)	DSM-5 ADOS-2	• n.r.	MDI	25 (22:3)	33-57 (45)	ASD

Study	Cases				Controls			
	N (M:F)	Age at intake in months (mean)	Diagnosis	Excluding criteria	Control Intervention	N (M:F)	Age at intake in months (mean)	Diagnosis
Vivanti et al., 2013	21 (20:1)	22-58 (38)	ADOS	• Severe medical conditions. • Significant vision, hearing, motor, or physical problems.	---	---	---	---
Vivanti et al., 2014*	27 (23:4)	18-60 (40)	ADOS	• CA < 18 or > 60 months.	CT	30 (27:3)	18-60 (42)	ASD

*Part of the sample was included in Vivanti et al., 2013.
ADOS: Autism Diagnostic Observation Schedule; ASD: Autism Spectrum Disorder; CA: Chronological Age; CT: Community Therapy; DSM: Diagnostic and Statistical Manual of Mental Disorders; MDI: Multidisciplinary Developmental Intervention; n.r.: not reported.

Table S5. Summary of ESDM studies excluded from our systematic review due to a patient recruitment age range beyond 48 months: intervention characteristics.

Study	Country	Study design	Setting	Intensity	Duration
Fulton et al., 2014	Australia	One group pretest-posttest design	• Centre-based (GS)	17-22 h/week	12 mo.
Geoffrey et al., 2019	France	One group pretest-posttest design	• Clinic-based • Home/Preschool/Nursery	4-10 (m=8) h/week	10 mo.
Laister et al., 2021	Austria	One group pretest-posttest design	• Centre/Home/Preschool	4.5 h/week	12 mo.
Robain et al., 2020	Switzerland	Case-control trial	• Not reported	20 h/week	12 mo.
Sinai-Gavrilov et al., 2020	Israel	Case-control trial	• Preschool-based (GS)	~44 h/week	8 mo.
Vivanti et al., 2013	Australia	One group pretest-posttest design	• Centre-based (GS)*	15-25 h/week	12 mo.
Vivanti et al., 2014	Australia	Case-control trial	• Centre-based (GS)*	15-25 h/week	12 mo.

GS: Group Setting.

Table S6. Summary of ESDM predictors of positive outcome in studies excluded due to a patient recruitment age range beyond 48 months.

Study	Predictors of better outcome	Improved functions correlated with predictors	Non-predictors
Fulton et al., 2014	• Higher IQ/DQ. • Lower ASD symptoms at intake. • VABS Daily Living Skills. • VABS Motor Skills/MSEL fine motor • VABS Communication • MSEL Receptive and Expressive Language	• Greater overall post-treatment improvement.	• VABS Socialization. • VABS Internalizing behaviors
Geoffrey et al., 2019	• Fine motor skills. • Non-verbal DQ.	• Post-treatment DQ.	• Age at intake. • Autism severity symptoms.
Laister et al., 2021	• Better social-communication behaviors. • Better verbal and non-verbal DQ.	• Overall verbal and non-verbal gains post-treatment.	• Age at intake. • Multilingualism. • Autism severity symptoms.
Robain et al., 2020	• Preference for social stimuli. • Younger age at intake. • Lower DQ at baseline. • Lower maladaptive behaviors.	• Post-treatment DQ.	• None reported.
Sinai-Gavrilov et al., 2020	• Lower symptoms severity. • Higher adaptive functioning. • Higher MSEL DQ.	• Overall treatment response: gain in MSEL Age Equivalent over pre-treatment DQ	• Age at start.

Study	Predictors of better outcome	Improved functions correlated with predictors	Non-predictors
Vivanti et al., 2013	• Functional use of objects. • Imitation. • Symptoms severity. • Goal understanding.	• Non-verbal skills. • Motor skills. • Language skills.	• Age at intake. • IQ. • Social attention.
Vivanti et al., 2014	• Lower symptoms severity.	• Post-treatment symptoms severity.	• Age at intake. • IQ. • Language skills. • Adaptive behaviors

ADOS: Autism Diagnostic Observation Schedule; ASD: Autism Spectrum Disorder; DQ: Developmental Quotient; IQ: Intellectual Quotient; MSEL: Mullen Scales of Early Learning; VABS: Vineland Adaptive Behavior Scale.

Supplementary References

Dimian, A. F., Symons, F. J., & Wolff, J. J. (2021). Delay to Early Intensive Behavioral Intervention and Educational Outcomes for a Medicaid-Enrolled Cohort of Children with Autism. Journal of autism and developmental disorders, 51(4), 1054–1066. https://doi.org/10.1007/s10803-020-04586-1

Eikeseth, S., Klintwall, L., Jahr, E., & Karlsson, P. (2012). Outcome for children with autism receiving early and intensive behavioral intervention in mainstream preschool and kindergarten settings. *Research in Autism Spectrum Disorders*, *6*(2), 829–835. https://doi.org/10.1016/j.rasd.2011.09.002

Eikeseth, S., Smith, T., Jahr, E., & Eldevik, S. (2002). Intensive behavioral treatment at school for 4- to 7-year-old children with autism. A 1-year comparison controlled study. *Behavior modification*, *26*(1), 49–68. https://doi.org/10.1177/0145445502026001004

Eikeseth, S., Smith, T., Jahr, E., & Eldevik, S. (2007). Outcome for children with autism who began intensive behavioral treatment between ages 4 and 7: a comparison controlled study. *Behavior modification*, *31*(3), 264–278. https://doi.org/10.1177/0145445506291396

Eldevik, S., Eikeseth, S., Jahr, E., & Smith, T. (2006). Effects of low-intensity behavioral treatment for children with autism and mental retardation. *Journal of autism and developmental disorders*, *36*(2), 211–224. https://doi.org/10.1007/s10803-005-0058-x

Eriksson, M. A., Westerlund, J., Hedvall, Å., Åmark, P., Gillberg, C., & Fernell, E. (2013). Medical conditions affect the outcome of early intervention in preschool children with autism spectrum disorders. *European child & adolescent psychiatry*, *22*(1), 23–33. https://doi.org/10.1007/s00787-012-0312-7

Flanagan, H. E., Perry, A., & Freeman, N. L. (2012). Effectiveness of large-scale community-based intensive Behavioral Intervention: A waitlist comparison study exploring outcomes and predictors. *Research in Autism Spectrum Disorders*, *6*(2), 673–682. https://doi.org/10.1016/j.rasd.2011.09.011

Frazier, T. W., Klingemier, E. W., Anderson, C. J., Gengoux, G. W., Youngstrom, E. A., & Hardan, A. Y. (2021). A Longitudinal Study of Language Trajectories and Treatment Outcomes of Early Intensive Behavioral Intervention for Autism. *Journal of autism and developmental disorders*, *51*(12), 4534–4550. https://doi.org/10.1007/s10803-021-04900-5

Fulton, E., Eapen, V., Crnčec, R., Walter, A., & Rogers, S. (2014). Reducing maladaptive behaviors in preschool-aged children with autism spectrum disorder using the early start denver model. *Frontiers in pediatrics*, *2*, 40. https://doi.org/10.3389/fped.2014.00040

Geoffray, M. M., Denis, A., Mengarelli, F., Peter, C., Gallifet, N., Beaujeard, V., Grosmaitre, C. J., Malo, V., Grisi, S., Georgieff, N., Magnificat, S., & Touzet, S. (2019). Using ESDM 12 hours per week in children with autism spectrum disorder: feasibility and results of an observational study. *Psychiatria Danubina*, *31*(3), 333–339. https://doi.org/10.24869/psyd.2019.333

Goin-Kochel, R. P., Myers, B. J., Hendricks, D. R., Carr, S. E., & Wiley, S. B. (2007). Early responsiveness to intensive behavioural intervention predicts outcomes among preschool children with autism. *International Journal of Disability, Development and Education*, *54*(2), 151-175. https://doi.org/10.1080/10349120701330404

Granpeesheh, D., Dixon, D. R., Tarbox, J., Kaplan, A. M., & Wilke, A. E. (2009). The effects of age and treatment intensity on behavioral intervention outcomes for children with autism spectrum disorders. *Research in Autism Spectrum Disorders*, *3*(4), 1014–1022. https://doi.org/10.1016/j.rasd.2009.06.007

Harris, S. L., & Handleman, J. S. (2000). Age and IQ at intake as predictors of placement for young children with autism: a four- to six-year follow-up. *Journal of autism and developmental disorders*, *30*(2), 137–142. https://doi.org/10.1023/a:1005459606120

Klintwall, L., & Eikeseth, S. (2012). Number and controllability of reinforcers as predictors of individual outcome for children with autism receiving early and intensive behavioral intervention: A preliminary study. *Research in Autism Spectrum Disorders*, *6*(1), 493-499. https://doi.org/10.1016/j.rasd.2011.07.009

Laister, D., Stammler, M., Vivanti, G., & Holzinger, D. (2021). Social-communicative gestures at baseline predict verbal and nonverbal gains for children with autism receiving the Early Start Denver Model. *Autism : the international journal of research and practice*, *25*(6), 1640–1652. https://doi.org/10.1177/1362361321999905

Lewon, A. B., & Ghezzi, P. M. (2021). An Evaluation of the Early Learning Measure as a Predictor of Outcomes in Early Intensive Behavioral Intervention. *Behavioral Interventions*, *36* (2), 388–406. https://doi.org/10.1002/bin.1768

Luiselli, J. K., Cannon, B. O., Ellis, J. T., Sisson, R. W. (2006). Home-Based Behavioral Intervention for Young Children with Autism/Pervasive Developmental Disorder. A Preliminary Evaluation of Outcome in Relation to Child Age and Intensity of Service Delivery. *Autism*, *4* (4), 426–438. https://doi.org/10.1177/1362361300004004007

Magiati, I., Charman, T., & Howlin, P. (2007). A two-year prospective follow-up study of community-based early intensive behavioural intervention and specialist nursery provision for children with autism spectrum disorders. *Journal of child psychology and psychiatry, and allied disciplines*, *48*(8), 803–812. https://doi.org/10.1111/j.1469-7610.2007.01756.x

Magiati, I., Moss, J., Charman, T., & Howlin, P. (2011). Patterns of change in children with autism spectrum disorders who received community based comprehensive interventions in their pre-school years: A seven year follow-up study. *Research in Autism Spectrum Disorders, 5*(3), 1016–1027. https://doi.org/10.1016/j.rasd.2010.11.007

Perry, A., Cummings, A., Geier, J. D., Freeman, N. L., Hughes, S., Managhan, T., Reitzel, J.-A., & Williams, J. (2011). Predictors of outcome for children receiving intensive behavioral intervention in a large, community-based program. *Research in Autism Spectrum Disorders*, *5*(1), 592–603. https://doi.org/10.1016/j.rasd.2010.07.003

Préfontaine, I., Morizot, J., Lanovaz, M. J., & Rivard, M. (2022). A person-centered perspective on differential efficacy of early behavioral intervention in children with autism: A latent profile analysis. *Research in Autism Spectrum Disorders*, *97*, 102017. https://doi.org/10.1016/j.rasd.2022.102017

Rivard, M., Morin, M., Mello, C., Terroux, A., & Mercier, C. (2019). Follow-Up of Children With Autism Spectrum Disorder 1 Year After Early Behavioral Intervention. *Behavior modification*, *43*(4), 490–517. https://doi.org/10.1177/0145445518773692

Robain, F., Franchini, M., Kojovic, N., Wood de Wilde, H., & Schaer, M. (2020). Predictors of Treatment Outcome in Preschoolers with Autism Spectrum Disorder: An Observational Study in the Greater Geneva Area, Switzerland. *Journal of autism and developmental disorders*, *50*(11), 3815–3830. https://doi.org/10.1007/s10803-020-04430-6

Sinai-Gavrilov, Y., Gev, T., Mor-Snir, I., Vivanti, G., & Golan, O. (2020). Integrating the Early Start Denver Model into Israeli community autism spectrum disorder preschools: Effectiveness and treatment response predictors. *Autism : the international journal of research and practice*, *24*(8), 2081–2093. https://doi.org/10.1177/1362361320934221

Smith, T., Klorman, R., & Mruzek, D. W. (2015). Predicting Outcome of Community-Based Early Intensive Behavioral Intervention for Children with Autism. *Journal of abnormal child psychology*, *43*(7), 1271–1282. https://doi.org/10.1007/s10802-015-0002-2

Stoelb, M., Yarnal, R., Miles, J., Takahashi, T. N., Farmer, J. E., & McCathren, R. B. (2004). Predicting responsiveness to treatment of children with autism: A retrospective study of the importance of physical dysmorphology. *Focus on Autism and Other Developmental Disabilities*, *19*(2), 66-77. https://doi.org/10.1177/10883576040190020101

Virues-Ortega, J., Rodríguez, V., & Yu, C. T. (2013). Prediction of treatment outcomes and longitudinal analysis in children with autism undergoing intensive behavioral intervention. *International Journal of Clinical and Health Psychology*, *13*(2), 91-100. https://doi.org/10.1016/S1697-2600(13)70012-7

Vivanti, G., Dissanayake, C., Zierhut, C., Rogers, S. J., & Victorian ASELCC Team (2013). Brief report: Predictors of outcomes in the Early Start Denver Model delivered in a group setting. *Journal of autism and developmental disorders*, *43*(7), 1717–1724. https://doi.org/10.1007/s10803-012-1705-7

Vivanti, G., Paynter, J., Duncan, E., Fothergill, H., Dissanayake, C., Rogers, S. J., & Victorian ASELCC Team (2014). Effectiveness and feasibility of the early start denver model implemented in a group-based community childcare setting. *Journal of autism and developmental disorders*, *44*(12), 3140–3153. https://doi.org/10.1007/s10803-014-2168-9

Waters, C. F., Amerine Dickens, M., Thurston, S. W., Lu, X., & Smith, T. (2020). Sustainability of Early Intensive Behavioral Intervention for Children With Autism Spectrum Disorder in a Community Setting. *Behavior modification*, *44*(1), 3–26. https://doi.org/10.1177/0145445518786463

Weiss, M. J. (1999). Differential rates of skill acquisition and outcomes of early intensive behavioral intervention for autism. *Behavioral Interventions*, *14*(1), 3–22. https://doi.org/10.1002/(SICI)1099-078X(199901/03)14:1<3::AID-BIN25>3.0.CO;2-F