Cognitive, language and behavioral outcomes in children in middle childhood with autism spectrum disorders exposed to early comprehensive treatment models: A meta-analysis and meta-regression

CURRENT STATUS: UNDER REVIEW

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DOI: 10.21203/rs.2.24508/v1

SUBJECT AREAS
Psychiatry

KEYWORDS
autism spectrum disorders, comprehensive treatment models, EIBI, ESDM,
outcomes, middle childhood, meta-analysis
Abstract

Background Early comprehensive treatment models (CTMs) have developed as effective treatments for children with autism spectrum disorder (ASD). Numerous studies have suggested that they can improve short-term outcomes, but little is known about middle childhood outcomes. The current meta-analysis reviewed studies reporting broader outcomes in middle childhood in children with ASD who ever participated in a CTM and examined the predictors of primary outcomes.

Methods We searched eight databases up to June 13, 2019, for relevant trials and natural experiments. Longitudinal studies were selected if they investigated the outcomes of CTMs in middle childhood in children with ASD. Two meta-analyses were undertaken to determine a summary estimate of change in treatment outcomes and evaluate the effect of CTMs; one used the standardized mean change between the pretest and posttest, and the other a classical meta-analysis. Stratified and random effects meta-regression analyses were performed to search for outcome differences among studies.

Results Eighteen intervention studies (involving 495 children with ASD) met all the inclusion criteria: 12 used early intensive behavioral intervention (EIBI) and two the Early Start Denver Model (ESDM). Outcomes were categorized into three parts: cognitive, language and behavioral (e.g., adaptive functioning and symptomatology). Overall, most children with ASD in middle childhood who participated in an early CTM make gains in many areas of functioning, especially with regard to symptom and language-related outcomes. Stratified analyses indicated that the ESDM displayed the largest effect on IQ improvement (ES=1.37, 95% CI: 0.95-1.80), while EIBI was more effective for symptom reduction (ES=-1.27, 95% CI: -1.96 to -0.58). Further meta-regression suggested that interventions with parent involvement and longer treatment hours yielded greater improvements in IQ and social adaptive functioning, respectively.

Conclusion The results demonstrate a positive association between CTMs and better prognosis in middle childhood, especially regarding symptoms and language. However, most of the extant research involves small, non-randomized studies, preventing definitive conclusions from being drawn. What is certain is that the outcomes in middle childhood of children with ASD are still far from normal,
especially for adaptive functioning, and the three mediating variables were treatment elements: approach, implementer and total treatment hours.

Background
Autism spectrum disorder (ASD) is a common neurodevelopmental disorder characterized by persistent deficits in social communication and repetitive, restricted patterns of behaviors and interests [1, 2]; it affects 1-2% of children [3, 4] and usually has a serious influence on development and lifetime costs [5]. At present, there are no curative or recommended therapies to treat all symptoms of ASD, but advances in behavioral treatments continue to be made [6]. Therapy has moved from isolated teaching episodes towards teaching in the natural environment, and a growing number of interventions are informed by child development theories [7].

A number of behavioral interventions, particularly for young children with ASD, have shown positive effects on cognition, language functioning and core symptoms [8, 9]; in most cases, only immediate outcomes at the end of the intervention or during the first 5 years of life were reported [10, 11]. However, even significant improvements in short-term outcomes do not fully establish treatment effectiveness because developmental gains could diminish after intensive services end [12]. Two narrative reviews that sought to clarify the long-term effects were limited due to the small number and poor quality of eligible follow-up studies [13, 14]. Robust studies on novel comprehensive treatment models (CTMs), such as Learning Experiences - An Alternative Program for Preschoolers and Parents (LEAP), are regarded as the key to long-term efficacy [6]. Thus, more subsequent trials in this field should be replicated and validated in different countries in the future.

It is likely that the increase in functional skills (i.e., intelligence) that allows children to gain more from later experiences is a long-term mediating mechanism allowing them to maintain gains [15], highlighting the importance of outcomes in each post-intervention period. However, there is limited understanding of outcomes post-middle childhood [16]. Previous findings regarding middle childhood cognitive ability and adaptive functioning outcomes in children with ASD have shown considerable variability. For example, Magiati et al [17] reported negative outcomes, but Este et al [12] reported the opposite. A recent meta-analysis indicated that almost half of individuals with ASD had poor
outcomes in later adolescence and adulthood [18], but we still lack any secondary research evidence focused explicitly on the outcomes in middle childhood.

Moreover, previous evidence indicates that study characteristics, children’s pretreatment levels, and treatment elements may affect the course of treatment and predict short-term outcomes [19], raising questions about the predictors of middle childhood outcomes. Both of the more well-established CTMs for ASD, referred to as early intensive behavioral intervention (EIBI) and the Early Start Denver Model (ESDM), are rooted in principles of applied behavior analysis (ABA). However, ESDM is also a parent-delivered, relationship-based intervention that fuses approaches validated by the science of child development, and there are few comparative evaluations of different programs [10]. If intervention approaches play a role, this role should not be underestimated. Besides, the transition to school and community is often difficult and stressful for individuals with ASD and their families, and in order to provide timely support, there is a pressing need for systematic knowledge of the middle childhood outcomes and their predictive factors in children with ASD who have been exposed to a CTM [20].

Above all, the present study aims to extend previous reviews by conducting a systematic review and meta-analysis of longitudinal studies from early childhood to middle childhood. The following goals were addressed: (1) report outcomes for specific domains of functioning and behavior (including cognition, language, adaptive functioning and symptomatology); (2) discover whether there are significant improvements in those outcomes for children with ASD, and the effect of the CTMs; and (3) examine the influence of childhood predictors, study characteristics and intervention elements on gains.

Methods
The protocol for this meta-analysis was registered in the PROSPERO database of prospectively registered systematic reviews (www.crd.york.ac.uk/PROSPERO; CRD42019146859), and the completed study conforms to the guidelines of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses [21].

Search Strategy And Selection Criteria
A systematic literature search was performed in eight electronic databases: PubMed, EMBASE,
PsycINFO, Scopus, the Cochrane Library, OVID, ERIC, and Web of Science. Each database was initially searched for relevant literature in English from its inception through June 13, 2019. We developed a search strategy for PubMed based on MeSH (Medical Subject Headings) terms and text words from key research that we identified a priori (see Table S1 for the full search strings). We reviewed the reference lists of key publications and relevant narrative reviews to identify studies that might have been missed in the database searches. To check for possible publication bias, we also undertook a gray literature search in clinical trial registries (http://www.ClinicalTrials.gov) using identical inclusion criteria to identify unpublished trials.

After the removal of duplicates, two independent investigators performed title scans and abstract reviews, and they screened the full-text articles to assess their eligibility for inclusion. Concordance among the investigators was satisfactory, with a positive agreement of 0.83; any disagreements between the authors were resolved by consultation with the third investigator. A number of prespecified inclusion and exclusion criteria were used to select key studies. The inclusion criteria were as follows: (a) randomized controlled trials (RCTs), quasi-experimental studies (i.e., nonequivalent control group design, one-group pre-test/post-test design), and natural experiments (a form of observational study in which the researcher cannot control or withhold the allocation of an intervention to particular areas or communities; thus, natural or predetermined variation in allocation occurs); (b) longitudinal studies with at least one assessment in early childhood and one in middle childhood or adolescence; (c) mean age of participants at first (“early child”) assessment < 5 years; (d) mean age of participants at last (“middle child or adolescent”) assessment ≥ 6 years; (e) professional/clinical diagnosis of ASD, autism, PDD-NOS, or Asperger syndrome based on DSM criteria; (f) English language articles published in a peer-reviewed journal (dissertations were excluded); and (g) articles assessing the effectiveness of a CTM and reporting some primary outcome variables focused on child functioning.

The following exclusion criteria were applied: (a) studies including children with medical complications or who were receiving drug treatment.; (b) pharmacological or dietary interventions, focused intervention practices (FIP, e.g., Pre-school Autism Communication Trial (PACT), Joint Attention,
Symbolic Play and Engagement Regulation (JASPER)), and other interventions with unclear evidence according to National Institute for Health and Care Excellence (NICE) guidance, such as secretin, chelation, or hyperbaric oxygen therapy; (c) studies reporting on a CTM that was not present in at least two other studies, that is “isolated intervention approaches”; and (d) pre- and posttest means and standard deviations were not available after attempts to contact the authors and could not be calculated from the descriptive data or statistical tests in the study manuscript. For multiple studies on the same cohort, we selected the publication with the longest follow-up, provided it included results with detailed demographic and intervention information.

Data Extraction And Quality Assessment Of The Included Studies

Pairs of investigators independently performed data extraction with a predesigned standardized form, and discrepancies were resolved by repeated discussion until consensus was reached. To ensure the accuracy and completeness of the extracted information, the third investigator repeatedly verified the extracted data abstraction for all the included studies. The following information from each included study was extracted: first author; region, study design, and year of publication; population characteristics at intake, including subtype of sample, age, and sex (% male); intervention characteristics, including intervention approaches (e.g., EIBI, ESDM), setting (clinical/home), delivery agent (therapists/parents), intensity and duration in weeks; type of comparison (e.g., treatment as usual, no comparison group); assessment times (i.e., pre, post, follow-up); the measures employed in each study; and the outcomes reported in middle childhood (e.g., autism symptomatology, IQ, adaptive behavior, language).

Two independent investigators applied the Evaluative Method for Determining Evidence-Based Practices in Autism to assess the quality of the included studies [22], which is available for many study designs. A previous study suggested that this tool can be applied to evaluate intervention studies and produce valid assessments of the empirical evidence on practices in children with ASD [23]. Six primary and eight secondary quality indicators were applied and are annotated in Table S3, including the characteristics of the participants, independent variables, dependent variables, comparison conditions, random assignment, blinding of raters, and fidelity. Divergence between the
two investigators who evaluated the quality of the studies was resolved by discussion. The quality of a study was assessed as “strong” when all the primary indicators received high quality ratings and there were four or more secondary indicators; “adequate” when more than four primary indicators received high ratings, with no unacceptable ratings and evidence of at least two secondary indicators; and “weak” otherwise.

Calculation Of Effect Sizes (ESS)

Because the instruments for evaluating a given outcome differed across studies (e.g., Wechsler Intelligence Scale for Children vs. Merrill-Palmer Scales of Mental Tests), we used standardized ESs to obtain standardized measurements of the effect of the intervention on the outcome variables.

According to the methodology of Reichow and Wolery [24], two types of ES were computed: the standardized mean change ES ($g_c$) and the standardized mean difference (SMD) ES ($g_d$). We took two steps to ensure the most conservative ES. First, ESs were calculated only when the data necessary for the calculation were available. If an outcome variable was missing the necessary data for the calculation of an ES, no ES was calculated for that outcome of the study. Hence, no data were extrapolated or interpolated for the calculation of ESs. Second, ESs based on small samples are known to be biased [25], so we multiplied them by the small sample correction factor [26].

The first ES analyses were calculated for the intervention groups in all the included studies and examined the differences between the average gains made by distinct samples. This comparison revealed the absolute difference within a sample from pre-intervention to middle childhood without regard to the comparison group in between-group studies. We calculated the $g_c$ by dividing each adjusted mean change by the pooled standard deviation.

For the between-group studies, the $g_d$ was used to show the magnitude of the difference between the group receiving a CTM and the comparison group. The ES ($g_d$) was calculated by dividing each adjusted mean difference by the pooled standard deviation.

Meta-analytic Procedures

We combined findings from all the included studies using prespecified meta-analytic methods to
determine the effect of CTMs in middle childhood in children with ASD. Two data synthesis steps: (1) Meta-analysis I was performed to estimate longitudinal changes in broader outcomes in middle childhood in children with ASD who were exposed to a CTM. (2) Meta-analysis II was performed to assess the effect of CTMs on those outcomes in the test group compared to the control group. The standardized mean change/difference and 95% confidence interval (CI) for each intervention effect were the primary outcome measures in the meta-analysis. Due to the diversity in population characteristics and intervention approaches, we expected a conservative estimation of the ESs. Consequently, a meta-analysis was performed on studies judged sufficiently similar and appropriate to pool using random effects models. Cohen’s criteria [27] were applied to determine the magnitude of the effect. The magnitude of the effect was assessed as “trivial” when the ES was < 0.2, “small” when the ES was between 0.2 and 0.49, “medium” when the ES was between 0.5 and 0.79, and “large” when the ES was ≥ 0.8.

Prespecified and exploratory stratified analyses were conducted to assess differences in ESs based on the use of (1) EIBI, (2) ESDM, and (3) other interventions to examine the consistency of the intervention approaches. Outcomes reported in fewer than six studies and parental outcomes were discarded from the meta-analysis, and studies were rank-ordered by quality rating in the forest plots. The $I^2$ statistic was used to assess the potential heterogeneity of ESs across interventions. An $I^2 > 50\%$ was considered evidence of heterogeneity. Sensitivity analysis was performed by reanalyzing the data using a fixed effects model and by omitting one study at a time to assess the impact of each individual study on the overall pooled estimate. Potential publication bias was assessed in two ways: a funnel plot and Egger’s linear regression test. When publication bias was identified, a nonparametric trim-and-fill method was used to adjust for the publication bias.

Meta-regression

Across 9 predictors in univariate meta-regressions (Table 3), three mediators of longitudinal change in middle childhood outcomes emerged: (1) EIBI was more effective in reducing symptom severity than non-EIBI programs, and this explained 64\% of the heterogeneity (Coefficient=-1.31, P = 0.045). (2) Higher total and social adaptive functioning were associated with longer total hours of the
intervention and explained 78% and 100% of the heterogeneity (Coefficient = 0.0001, P = 0.021; Coefficient = 0.0002, P = 0.032, respectively). (3) Higher social adaptive functioning was also associated with a higher risk of bias (Adj R² = 100.00%, Coefficient = 0.78, P = 0.026). No potential confounding factors affected the change in DLS. Regarding the multivariate meta-regressions, they demonstrated a clear effect of delivery agent (therapist or therapist and parents) on IQ after the p-value was adjusted (P = 0.028, Table 4). Specifically, the involvement of parents in implementing intervention strategies had a more beneficial effect on IQ enhancement than the involvement of a therapist alone.

Table 3
Results of the univariate meta-regression analyses by adaptation and symptomatic variables.

|                     | ASD SS | Composite[d] | DLS | Social |
|---------------------|--------|--------------|-----|--------|
|                     | Coeff  | Coeff        | Coeff | Coeff  |
| Internal Validity   |        |              |      |        |
| Risk of bias        | 1.100  | 0.33         | 0.450| 0.16   | 0.019 | 0.97 | 0.780 | 0.03* |
| Sample size         | 0.020  | 0.41         | -0.014| 0.15   | -0.037| 0.63 | -0.033| 0.62  |
| Population Characteristics |      |              |      |        |
| Pre age             | -0.080 | 0.17         | -0.018| 0.48   | -0.046| 0.46 | -0.027| 0.61  |
| Pre IQ              | -0.029 | 0.75         | 0.001| 0.98   | -0.014| 0.74 | 0.011 | 0.83  |
| Time interval[a]    | -0.002 | 0.85         | -0.002| 0.65   | 0.009 | 0.53 | -0.022| 0.03  |
| Post age[b]         | -0.005 | 0.64         | -0.001| 0.89   | 0.0006| 0.98 | -0.039| 0.05  |
| Intervention Characteristics |      |              |      |        |
| Approaches[c]       | -1.310 | 0.05*        | -0.704| 0.18   | -0.550| 0.30 | 0.330 | 0.47  |
| Total treatment hours| -0.0002| 0.19         | 0.0001| 0.02*  | -0.0001| 0.82 | 0.0002| 0.03* |
| Delivery agents     | 1.180  | 0.15         | 0.097| 0.77   | 0.120 | 0.84 | 0.033 | 0.95  |

Notes:
- a Time interval between postintervention and follow-up.
- b Mean age of participants at last (“middle child or adolescent”) assessment.
- c Categorical variable, EIBI = 1, non-EIBI (ESDM and other interventions) = 0.
- d Based on the result of sensitivity analysis, Magiati (2011) was removed in the meta-regression analyses.

ASD SS, ASD symptom severity; Coeff, unstandardized meta-regression coefficient; Composite, Vineland adaptive composite score; DLS, Daily living skills; Pre, preintervention.

* P ≤ 0.05

ASD symptom severity - Approaches: Adj R² = 64.19%
Vineland adaptive composite score - Total treatment hours: Adj R² = 78.06%
Vineland social adaptive score - Total treatment hours: Adj R² = 100.00%
Vineland social adaptive score - risk of bias: Adj R² = 100.00%
Table 4

Results of the multivariate meta-regression analyses by cognitive function.

|           | Coefficient | SE     | 95% CI          | P    | tau²  | k | Adj R² (%) | Model P | Type I errors¹ |
|-----------|-------------|--------|-----------------|------|-------|---|------------|---------|----------------|
| IQ        | 0.6756      | 0.2637 | [0.0881, 1.2632] | 0.028* |       |   |            |         |                |
| Delivery agentsb | -0.0289     | 0.0204 | [-0.0742, 0.0165] | 0.187 | 0.1294 | 14 | 52.15      | 0.048*  | not            |
| Pre age   |             |        |                 |      |       |   |            |         |                |
| Total treatment hours | 0.000001 | 0.000046 | [-0.0001, 0.0001] | 0.969 |       |   |            |         |                |

Notes: a Monte Carlo permutation test was applied to correct type I errors for multiple covariate meta-regressions. b Categorical variable: therapist = 1, therapist + parents = 2.

CI, confidence interval; Coefficient, unstandardized meta-regression coefficient; CTM, comprehensive treatment model; IQ, intelligence quotient; k, number of studies or "clusters"; Pre, preintervention; SE, standard error.

* p ≤ 0.05

Results

Literature Search and Study Characteristics

A flow diagram detailing the selection process is presented in Fig. 1. We identified 8,725 potentially relevant citations, and 174 full citations were retrieved. Overall, 18 unique citations were deemed eligible for the systematic review and meta-analysis [12, 17, 28-44].

A systematic description of eight between-group studies and ten pre-post studies (including 495 non-overlapping participants with ASD) is provided in Table 1. Three of the ten pre-post studies with within-subject designs were natural experiments, and the intervention characteristics were reported by parents. Half of the included studies were post-intervention follow-ups and thus had a period of time during which the intervention was not being implemented; the outcomes from these studies were defined as “long-term”. These studies used a wide range of measures to assess autism symptom severity, cognitive and language abilities, and adaptive behavior (Table S2). Most employed standardized measures and researcher-developed interviews, and all the repeatedly measured outcomes were standard scores. Moreover, six studies (33%) received the highest rating (strong), two (11%) received the middle rating (adequate), and ten studies (56%) received the lowest rating (weak; Table S3) based on the assessment of research report rigor.
Table 1
Characteristics of the studies included in the meta-analysis reporting multiple outcomes in children in middle childhood with ASD.

| Study            | Region | Design | Sample | Participants | Intervention characteristics | Controls | Rigor rating |
|------------------|--------|--------|--------|--------------|-----------------------------|----------|--------------|
| Akshoff et al (2010) | USA    | Pre-post experimental | 20 (90.00%) | AD PDD-NOS (DSM-IV) | 28.90 --- | others | 31.00 | 7.70 | T+P | 85.3 | NO | Weak |
| Bibby et al (2002)  | UK     | Pre-post Observational | 22 (83.33%) | AD PDD-NOS | 43.40 45.50 | EIBI (UCLA) | 30.30 | 31.60 | 33.20 | T | 77.4 | 78.7 | NO | Weak |
| Clark et al (2017)  | AUS    | Pre-post Observational | 48 (75%) | AD ASD (DSM-IV) | 25.45 63.61 | others | NR | NR | T | 96.5 | NO | Weak |
| Cohen et al (2006)  | USA    | Between-group NRT | 21 (85.71%) | AD PDD-NOS | 30.20 61.60 | EIBI (UCLA) | 35-40 | 36.00 | T+P | 66.2 | YES | N-R | Strong |
| Estes et al (2015)  | USA    | Between-group RCT | 21 (85.19%) | AD PDD-NOS (DSM-IV) | 23.90 61.00 | ESDM | 31.50 | 24.00 | T+P | 72.9 | YES | Random | Strong |
| Gabriels et al (2001) | USA    | Pre-post Observational | 48 (70.59%) | Autism PDD-NOS (DSM-IVTR) | 30.60 57.81 | others | 22.63 | 36.00 | T | 68.7 | NO | Weak |
| Harris et al (2000) | USA    | Pre-post experimental | 27 (85.19%) | AD PDD-NOS (DSM-III-R) | 49.00 59.33 | EIBI | 35-45 | 36.00 | T+P | 85.0 | NO | Weak |
| Howard et al (2014) | USA    | Between-group NRSI Observational | 29 (86.00%) | AD PDD-NOS (DSM-IV) | 30.86 60.57 | EIBI (IBT) | 35-40 | 37.90 | T+P | 69.2 | YES | N-R | Strong |
| Kovshoff et al (2011) | UK      | Between-group NRT | 23 (81.25%) | Autism | 35.70 61.43 | EIBI | 25.60 | 24.00 | T+P | 83.7 | YES | N-R | Adequate |

(Continued)

| Study            | Region | Design | Sample | Participants | Intervention characteristics | Controls | Rigor rating |
|------------------|--------|--------|--------|--------------|-----------------------------|----------|--------------|
| Landa et al (2012) | USA    | Pre-post | 48 (81.25%) | ASD | 27.00 60.10 | others | 10.00 | 6.00 | T+P | 72.6 | No | Weak |
| Study                        | Country | Study Type       | Pre/Post | Post IQ | Post Age | Intervention Characteristics | Post Therapist | Notes                                                                 |
|------------------------------|---------|------------------|----------|---------|----------|-----------------------------|----------------|----------------------------------------------------------------------|
| McEachin et al. (1993)       | USA     | Between-group NRT | 84.21%   | 34.60   | 53.00    | EIBI (UCLA)                 | T + P          | Yes                                                                   |
| Magiat et al. (2011)         | UK      | Pre/post experi  | 36       | 38.90   | 64.40    | EIBI (UCLA)                 | T              | No Weak                                                             |
| Perry et al. (2017)          | CA      | Pre/post experi  | 90.48%   | 40.92   | ---      | EIBI                        | T              | Yes                                                                   |
| Salows et al. (2005)         | USA     | Between-group RCT | 84.61%   | 33.23   | 50.85    | EIBI (UCLA)                 | T              | Yes Rando                                                            |
| Smith et al. (2000)          | USA     | Between-group RCT | 80.00%   | 36.07   | 50.53    | EIBI (UCLA)                 | T              | Yes Adequate                                                         |
| Smith et al. (2015)          | USA     | Pre/post experi  | 84.51%   | 39.12   | 58.80    | EIBI (UCLA)                 | T              | No Weak                                                             |
| Vinen et al. (2017)          | AUS     | Between-group NRSI | 87.10%   | 39.16   | 55.42    | ESDM ≥ 15                   | T + P          | Yes N-R                                                             |
| Weiss and Delmolino (2006)   | USA     | Pre/post experi  | 95.00%   | 41.50   | ---      | EIBI (IBT)                  | T              | No Weak                                                             |

Notes: a Total number of subjects at the last measurement for pre-post studies and subjects in the experimental group for between-group studies.  
b Chronological age at which the participants entered the study or started the intervention.  
c Intervention characteristics for pre-post studies and the experimental group’s features for between-group studies.  
d The quality assessment was examined by the Evaluative Method for Determining Evidence-Based Practices in Autism (Reichow, 2011).  
e Others (other interventions) refers to the combination of standard interventions, including discrete trial training, incidental teaching, pivotal response training, structured teaching and the picture exchange communication system (e.g., community, inclusive intervention).  
f The samples are inconsistent between the two outcomes reported by Bibby et al. (2002).  
g Sufficient data were acquired from the figures in Cohen et al. (2006).  
h The early learning composite (ELC) from MSEL was used to report cognition function.  
i Gabriels et al. (2001) was a retrospective case-control study conducted on one sample receiving the same treatment and examined the influencing factors of the best outcomes.  
j Two reports, Lovaas (1987) and McEachin et al. (1993), used the same participants. The McEachin et al. (1993) report was used because it had the longest follow-up.  
k Male% was not reported in follow-up subjects. We used male% at intake to replace it.

Population And Intervention Characteristics

The mean pre-IQ, reported in 15 studies, was 50-64; the mean pretest age was 24-49 months, and
the mean age at the last assessment was 66–192 months. Of the 18 studies included, 12 conducted EIBI (seven applied the UCLA model [36]), two used the ESDM, and four used other interventions. Other interventions (e.g., community intervention) refers to the combination of standard interventions. With regard to the intervention characteristics, eight studies were implemented by therapists and parents. The intervention duration and intensity ranged from 6 to 60 months and from 15 to 40 weekly hours, respectively. Six studies reported that participants were receiving supplemental treatments. Moreover, the comparison conditions in the eight between-group studies, which included 6 EIBI programs and 2 ESDM programs, were treatment as usual (k = 5), different agents (k = 2) and active comparison (k = 1).

Outcomes And Meta-analysis I: Longitudinal Change In Middle Childhood

Although a number of studies evaluated outcomes across multiple domains, others focused on specific areas, such as intellectual abilities, adaptive functioning, language outcomes or autism severity. A summary of reported outcomes is presented in Table 2; generally, positive ESs ($g_c$) suggest that children’s performance improved on average after the preintervention stage in multiple dimensions of functioning (see Fig. 2 and Fig. 3).
Table 2
Summary of cognitive, language, symptomatic and adaptive functioning outcomes in middle childhood.

| Study | IQ | Expressive language | ASD Symptom Severity | Adaptation composite |
|-------|----|---------------------|----------------------|----------------------|
|       | Preintervention | Middle childhood | Preintervention | Middle childhood | Preintervention | Middle childhood | Preintervention | Middle childhood |
| Bibby | 50.80 ± 20.60 | 55.00 ± 22.30 | 54.50 ± 13.00 | 63.40 ± 21.90 |
| Clark | 65.68 ± 11.87 | 102.71 ± 19.55 | 6.45 ± 2.08 | 6.20 ± 2.68 |
| Cohen | 61.60 ± 9.20 | 55.00 ± 22.30 | 52.90 ± 14.50 | 29.80 ± 29.91 |
| Estes | 61.00 ± 25.88 | 87.00 ± 25.26 | 6.45 ± 2.08 | 6.20 ± 2.68 |
| Harris | 61.43 ± 16.43 | 80.65 ± 23.99 | 49.73 ± 16.34 | 29.88 |
| Howard | 61.60 ± 16.40 | 80.65 ± 23.99 | 49.73 ± 16.34 | 30.29 |
| Kovshof | 61.60 ± 16.40 | 80.65 ± 23.99 | 49.73 ± 16.34 | 30.29 |
| Landa | 61.60 ± 16.40 | 80.65 ± 23.99 | 49.73 ± 16.34 | 30.29 |
| McEachin | 53.00 ± 13.00 | 74.50 ± 24.40 | 6.45 ± 2.08 | 6.20 ± 2.68 |
| Magiati | 64.40 ± 30.00 | 52.60 ± 21.80 | 2.60 ± 7.30 | 34.50 ± 37.90 |
| Perry | 61.60 ± 16.40 | 80.65 ± 23.99 | 49.73 ± 16.34 | 29.88 |
| Sallove | 61.60 ± 16.40 | 80.65 ± 23.99 | 49.73 ± 16.34 | 29.88 |
| Smith | 61.60 ± 16.40 | 80.65 ± 23.99 | 49.73 ± 16.34 | 29.88 |
| Smith | 61.60 ± 16.40 | 80.65 ± 23.99 | 49.73 ± 16.34 | 29.88 |
| Vinen | 55.42 ± 8.74 | 76.06 ± 20.82 | 7.39 ± 2.09 | 7.97 ± 2.60 |
| Weiss | 61.60 ± 16.40 | 80.65 ± 23.99 | 49.73 ± 16.34 | 29.88 |

Note: a Data were acquired from the merging of subgroups in Clark et al. (2017).

b Data were acquired from the figures in Cohen et al. (2006).

c The standard deviation is calculated from the range of the outcomes in Estes et al. (2015) and McEachin et al. (1993).

Akshoomoff et al. (2010) reported the subdomains of adaptive functioning and intellectual functioning, which are not represented in Table 2.

ASD, autism spectrum disorder; IQ, intelligence quotient.

The pooled standardized mean change ES for IQ, covering 420 participants, was 0.85 (95% CI: 0.47–1.22). Only one study [17] had a negative ES for IQ, while ten of the other samples yielded an ES for IQ equal to or greater than 0.50. Five EIBI studies reported data on language skills, four of which reported favorable effects on both expressive and receptive language. The pooled ESs for expressive language and receptive language were 1.12 (95% CI: 0.70–1.53) and 1.11 (95% CI: 0.83–1.40), respectively. Regarding the longitudinal changes in ASD symptom severity, seven studies reported relevant data, and three of them showed a favorable effect. The pooled ES was −0.68 (95% CI: -1.24–0.12). For adaptive functioning, the subdomains showed heterogeneity (Fig. 3). A medium ES was
found for both communication (ES = 0.75, 95% CI: 0.47–1.02) and social (ES = 0.55; 95% CI: 0.17–0.92), whereas a trivial ES was found for daily living skills (DLS) (ES=-0.05, 95% CI: -0.49-0.39) and composite score (ES = 0.15, 95% CI: -0.28-0.57).

Meta-Analysis II: Effects of EIBI on Middle Childhood Outcomes Compared to those in the Control Group

As presented in Fig. 4, the majority of the SMD ESs (g_d) were positive, which indicates that the functioning of children with ASD in the EIBI group was generally better than that in the comparison group in multiple dimensions. In line with the longitudinal change results, EIBI had small to medium effects in terms of improving IQ (ES = 0.53, 95% CI: 0.16–0.90), communication (ES = 0.38, 95% CI: 0.03–0.73), and social (ES = 0.38, 95% CI: 0.03–0.73). The ES for DLS was also nonsignificant in four studies (ES = 0.18; 95% CI: -0.16-0.53). However, we failed to find a favorable improvement in expressive and receptive language when the analysis was applied solely to controlled studies (ES = 0.46, 0.42; 95% CI: -0.08-1.0, -0.06-0.91, respectively). Additionally, adaptation composite scores were reported in five studies, resulting in a significant effect size of 0.47 (95% CI 0.11 to 0.83).

The controlled ESDM studies and the outcome for ASD symptom severity were discarded from meta-analysis II because of inadequate or isolated data.

Stratified Analyses

The results for the comparison of the three intervention approaches in the stratified analyses of meta-analysis I revealed disparate effects. Notably, the ESDM group had a significantly higher ES for IQ than the EIBI and other interventions groups (g_c=1.37, 0.61 and 1.21, respectively; Fig. 2). Regarding other outcomes, the number of ESDM studies is insufficient for comparison. Nevertheless, the opposite occurred for symptom outcomes (ASD symptom severity and social adaptive functioning), as the EIBI group had clearly greater symptom improvement than the other interventions group (g_c=-1.27, 0.65 vs. g_c=-0.03, 0.19). Additionally, stratified analyses could not be conducted in meta-analysis II because of the limitations of the controlled studies.

Sensitivity Analysis
Sensitivity analyses suggested that the estimates were not substantially modified by any single study. There was an exception for the adaptive composite score, as a small effect with a \( g_c \) of 0.31 (95% CI 0.002 to 0.62) was shown when Magiati [17] was removed in meta-analysis I. The sensitivity analyses did not yield different findings after the data were reanalyzed using a fixed effects model.

Publication Bias

No sign of publication bias was found in the funnel plots and Egger’s test for any outcome.

Discussion

To our knowledge, this is the first comprehensive study to systematically and quantitatively assess a series of developmental and symptom outcomes for children with ASD in middle childhood. Overall, we found positive effects of early CTMs on longitudinal change in intelligence, language development, communication and social adaptation, and core symptom severity in children with ASD in middle childhood but negligible effects on DLS and total adaptative behavior. In addition, there is preliminary evidence to suggest that children in middle childhood in the EIBI group have made greater gains than children in the control group. However, it is noteworthy that the outcomes in middle childhood and the risk of bias in most of the included studies are not optimistic.

The findings from this study are similar to those of a narrative review that examined the long-term effects of early intervention (EI) in primary school [14]. The review included eight eligible studies, 5 of which were also included in our study. Both this review and the narrative review indicate that most children with ASD who have ever participated in a CTM make gains in many areas of functioning. However, only 9 long-term follow-up studies were found based on our inclusion and exclusion criteria. In other words, the number of well-designed longitudinal studies is still inadequate to determine middle childhood outcomes and even long-term effects.

Although favorable effects were apparent across most outcomes, language-related outcomes (IQ, receptive language, expressive language, and communication adaptation) were distinctly superior to social adaptation and ASD symptom severity, with ESs approaching 1.2 for receptive and expressive language. This finding is highly consistent with previous findings from a meta-analysis on the effects of ABA intervention in early childhood that included studies with a minimum intervention duration of
one year [45] and has been attributed to the amount of time devoted by most behavioral interventions to language and communication skills [46].

In addition, there is some evidence that EIBI leads to a small to moderate effect in youth with ASD compared to the effect of treatment as usual, parent-mediated or minimal treatment controls in terms of IQ and Vineland social, communication, and adaptive composite scores. This is particularly noteworthy because these ESs were smaller than those from a Cochrane Collaboration systematic review and meta-analysis of studies comparing EIBI to treatment as usual in the community [47], which found medium to large significant positive effects. The comparison types of the controlled studies varied across the included studies, with nearly half of them involving implementer comparison (therapist vs. therapist and parents); stratification by comparison type was impossible due to the very small number of studies. Actually, the available evidence has proven the effectiveness of parent-mediated EI, showing improvement comparable with that achieved with therapist-mediated EI [48]. Needless to say, the existence of this comparison type would weaken the ES.

It is generally believed that children participating in early CTMs will have a reduced need for support and programs as they go through school [43], but our study highlighted that despite some improvements, the outcomes in middle childhood of children with ASD are still far from normal. Thus, ongoing intervention is necessary, especially for adaptive functioning in real life. Even so, almost 30% of US children with ASD did not receive behavioral or medication treatment [49], and multiple gaps were identified across all the stages of intervention development and testing from conceptualization to community implementation [50]. These may be crucial issues to fill to improve outcomes for individuals with ASD in the future.

Furthermore, a systematic review [16] of outcomes in late adolescence and adulthood was selected for comparison with our results to draw more reliable conclusions, and improvements in language and symptom outcomes were found in both children and adult populations. Our results, however, showed a significant gain in IQ and negative findings for adaptive functioning and DLS. Analyses of the distinctiveness of developmental trajectories with respect to these outcomes provided evidence of steady and remarkable improvements in verbal and nonverbal IQ from childhood to adolescence when
the pre-IQ range in the included studies was 50–60 [51]. Similarly, individuals with moderate adaptive functioning at baseline (standard score of approximately 75) had a stable trajectory [52]. These findings suggest that longitudinal change could be influenced somewhat by the baseline level of participants, and our result explains the prognosis of ASD children with moderate functioning in terms of IQ and adaptation at baseline. Viewed from another angle, we did not find enough studies reporting the prognosis of lower- and higher-functioning ASD. Regarding the negative findings for DLS, Di Rezze et al indicated that an improvement in trajectory was associated only with lower and improving ASD symptom severity [53], whereas none of the seven studies reported symptom-related data. Moreover, we did not find any statistically significant factors among the nine available variables in the meta-regression. Therefore, developmental and symptom outcomes could affect each other over time, and the effectiveness of CTMs should be examined by controlled studies designed for multiple subpopulations. Furthermore, the environmental factors that may be associated with continued changes in those outcomes from childhood to adulthood remain largely unknown [54] and may be responsible for the difference in the results.

Due to the variation in middle childhood changes, we sought to explore the sources. Although the ESDM was the most effective in improving IQ and EIBI showed greater efficacy in ASD symptom severity reduction in affected children, we are still far from establishing an evidence basis for the superiority or inferiority of the ESDM program because of the limited number of appropriately designed relevant studies. However, meta-regression provided a clear account of the impact of the delivery agent and intervention approach and verified the results of the stratified analyses: 1) IQ tended to benefit more from intervention programs mediated by parents and therapists, while the ESDM is an intervention strategy implemented by parents; 2) symptoms tended to benefit more from EIBI programs than non-EIBI programs. We did explore whether the quality and sample size of the studies, initial IQ or age of participants were related to deterioration/improvement in all outcomes over time. Only four significant associations were identified: delivery agents, total treatment hours, intervention approach and risk of bias; these derive almost entirely from intervention elements.

Limitation
The conclusions of this review should be interpreted with caution in light of its limitations. As can be seen, very few high-quality studies specifically examine outcomes in middle childhood, and the numerous methodological weaknesses of the studies reviewed here limit the conclusions that can be drawn. Given that the studies varied widely in terms of cohort selection, treatment features, and assessment reliability, we could not establish an unbiased way of taking into account all these factors in judging research quality. We strongly endorse the conclusions of some reviews that rated the overall quality of evidence as ‘low’ or ‘very low’ using the GRADE system [6]. However, according to the current quality assessment, the quality level necessary to perform meta-regression was met, and most of the changes in the outcome have nothing to do with the quality. The only pity is that the LEAP program [55], which has a rigorous research-based design, was excluded from this review because of insufficient initial data. Second, to achieve a certain statistical power, this study combined single-group pre-post studies with between-group controlled studies, while there was somewhat controversial. Thus, we also performed the meta-analysis II of the between-group studies only, which showed relatively consistent results. Finally, fidelity measures and standards cannot currently be assumed for studies in this field, and most did not provide information about additional treatment received after the intervention services ended.

Recommendations For Future Research
In sum, recommendations for clinicians and researchers planning to conduct empirical studies in this area include the following: (1) employ study designs that use randomized controlled trials whenever possible and match treatment intensity and duration across groups; (2) record the specific intervention approaches and components in detail and monitor the fidelity of the intervention process; (3) collect detailed information on education and intervention strategies applied during middle childhood; (4) due to the current need, explore ESDM programs and lower- and higher-functioning ASD; and (5) focus on follow-up measurement and record the initial measurement as comprehensively as possible.

Conclusion
Overall, there is some evidence that most children with ASD who participated in an early CTM make
gains in many areas of functioning by middle childhood, especially with respect to symptom- and language-related outcomes. However, most of the existing research relies on small studies that are non-randomized, forestalling definitive conclusions. What is certain is that the middle childhood outcomes of children with ASD are still far from normal, especially for adaptive functioning, and the mediating variables of intervention efficacy were primarily intervention elements, including approach, implementer and total treatment hours. Furthermore, the ESDM displayed the largest effect in terms of improving intelligence development, and EIBI showed greater efficacy in reducing ASD symptom severity.

Abbreviations

ABA
Applied Behavior Analysis;

ASD
Autism Spectrum Disorder;

CI
Confidence Interval;

CTM
Comprehensive Treatment Model;

DLS
Daily Living Skills;

DSM
The Diagnostic and Statistical Manual of Mental Disorders;

EIBI
Early Intensive Behavioral Intervention;

ES
Effect Sizes;

ESDM
Early Start Denver Model;

FIP
Focused Intervention Practices;

GRADE
Working Group Grades of Evidence;

IQ
Intelligence Quotient;
JASPER
Joint Attention, Symbolic Play and Engagement Regulation;
LEAP
Learning Experiences - An Alternative Program for Preschoolers and Parents;
MeSH
Medical Subject Headings;
NICE
National Institute for Health and Care Excellence;
PACT
Pre-school Autism Communication Trial;
RCT
Randomized Controlled Trial;
SMD
Standardized Mean Difference;
UCLA
University of California, Los Angeles;
VABS
Vineland Adaptive Behavioral Scales.

Declarations

Acknowledgements

Not Applicable.

Funding

Financial support for this research was provided by the National Natural Science Foundation of China (Grant No. 81872639) and the Key Realm R&D Program of Guangdong Province (2019B030335001).

Availability of data and materials

This is an evidence synthesis study, all data is available from the primary research studies, or can be circulated from the corresponding author.
Authors’ contributions

BJS, LC and JJ were involved in the conception and design of the review. BJS, WJW and MXD contributed to the data collection. JJZ and JYL contributed to the quality assessment. BJS and JJZ conducted the meta-analyses. BJS and MXD contributed to interpretation of data. The review was conducted by BJS and WJW, who completed initial drafts of the paper. LC, BW and JJ gave critical comments and advice that helped shape the review. All authors read and approved the final manuscript.

Ethics approval and consent to participate

The protocol for this meta-analysis was registered in the PROSPERO database of prospectively registered systematic reviews (www.crd.york.ac.uk/PROSPERO; CRD42019146859).

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

References

1. American PA: Diagnostic and statistical manual of mental disorders (DSM-5®): American Psychiatric Pub; 2013.

2. Lord C, Elsabbagh M, Baird G, Veenstra-Vanderweele J: Autism spectrum disorder. Lancet 2018, 392(10146):508-520.

3. Baio J, Wiggins L, Christensen DL, Maenner MJ, Daniels J, Warren Z, Kurzius-Spencer M, Zahorodny W, Robinson RC, White T et al: Prevalence of Autism Spectrum Disorder Among Children Aged 8 Years - Autism and Developmental Disabilities Monitoring Network, 11 Sites, United States, 2014. MMWR Surveill
4. Lai MC, Lombardo MV, Baron-Cohen S: *Autism*. LANCET 2014, 383(9920):896-910.

5. Buescher AV, Cidav Z, Knapp M, Mandell DS: **Costs of autism spectrum disorders in the United Kingdom and the United States.** JAMA PEDIATR 2014, 168(8):721-728.

6. Reichow B, Hume K, Barton EE, Boyd BA: **Early intensive behavioral intervention (EIBI) for young children with autism spectrum disorders (ASD).** Cochrane Database Syst Rev 2018, 5:D9260.

7. Wetherby AM, Guthrie W, Woods J, Schatschneider C, Holland RD, Morgan L, Lord C: **Parent-implemented social intervention for toddlers with autism: an RCT.** PEDIATRICS 2014, 134(6):1084-1093.

8. Boyd RD, Corley MJ: **Outcome survey of early intensive behavioral intervention for young children with autism in a community setting.** AUTISM 2001, 5(4):430-441.

9. Dawson G, Rogers S, Munson J, Smith M, Winter J, Greenson J, Donaldson A, Varley J: **Randomized, controlled trial of an intervention for toddlers with autism: the Early Start Denver Model.** PEDIATRICS 2010, 125(1):e17.

10. Magiati I, Tay XW, Howlin P, Correspondence A, I. Magiati DOPN, As ALSS, Sg PNE: **Early comprehensive behaviorally based interventions for children with autism spectrum disorders: A summary of findings from recent reviews and meta-analyses.** Neuropsychiatry 2012, 2(6):543-570.

11. Tonge BJ, Bull K, Brereton A, Wilson R: **A review of evidence-based early intervention for behavioural problems in children with autism spectrum disorder: the core components of effective programs, child-focused interventions and comprehensive treatment models.** Curr Opin Psychiatry 2014,
12. Estes A, Munson J, Rogers SJ, Greenson J, Winter J, Dawson G: Long-Term Outcomes of Early Intervention in 6-Year-Old Children With Autism Spectrum Disorder. *J AM ACAD CHILD PSY* 2015, 54(7):580-587.

13. Matson JL, Konst MJ: What is the evidence for long term effects of early autism interventions? *RES AUTISM SPECT DIS* 2013, 7(3):475-479.

14. Starr EM, Popovic S, McCall BP: Supporting children with autism spectrum disorder at primary school: Are the promises of early intervention maintained? *Current Developmental Disorders Reports* 2016, 3(1):46-56.

15. Ramey CT, Ramey SL: Early intervention and early experience. *AM PSYCHOL* 1998, 53(2):109.

16. Magiati I, Tay XW, Howlin P: Cognitive, language, social and behavioural outcomes in adults with autism spectrum disorders: A systematic review of longitudinal follow-up studies in adulthood. *CLIN PSYCHOL REV* 2014, 34(1):73-86.

17. Magiati I, Moss J, Charman T, Howlin P, Correspondence A, I. Magiati DOPN, As ALSS, Sg PNE: 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. 2011, 5(3):1016-1027.

18. Steinhausen HC, Mohr Jensen C, Lauritsen MB: A systematic review and meta-analysis of the long-term overall outcome of autism spectrum disorders in adolescence and adulthood. *ACTA PSYCHIAT SCAND* 2016, 133(6):445-452.

19. Tiura M, Kim J, Detmers D, Baldi H: Predictors of longitudinal ABA treatment outcomes for children with autism: A growth curve analysis. *RES DEV DISABIL*
2017, *70*:185-197.

20. Walker S, Dunbar S, Meldrum K, Whiteford C, Carrington S, Hand K, Berthelsen D, Nicholson J: *The transition to school of children with developmental disabilities: Views of parents and teachers*. *AUST J EARLY CHILD* 2012, **37**(3):22-29.

21. Moher D, Liberati A, Tetzlaff J, Altman DG: *Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement*. *ANN INTERN MED* 2009, **151**(4):264-269.

22. Reichow B, Volkmar FR, Cicchetti DV: *Development of the evaluative method for evaluating and determining evidence-based practices in autism*. *J AUTISM DEV DISORD* 2008, **38**(7):1311-1319.

23. Reichow B, Doehring P, Cicchetti DV, Volkmar FR: *Evidence-based practices and treatments for children with autism*: Springer Science & Business Media; 2010.

24. Reichow B, Wolery M: *Comprehensive synthesis of early intensive behavioral interventions for young children with autism based on the UCLA young autism project model*. *J AUTISM DEV DISORD* 2009, **39**(1):23-41.

25. Lipsey MW, Wilson DB: *Practical meta-analysis*. Sage Publications, Inc; 2001.

26. Hedges LV, Olkin I: *Statistical methods for meta-analysis*. *New Directions for Program Evaluation* 1985, **1984**(24):25-42.

27. Cohen J: *Statistical power analysis for the behavioral sciences*. *TECHNOMETRICS* 1988, **31**(4):499-500.

28. Akshoomoff N, Stahmer AC, Corsello C, Mahrer NE: *What Happens Next? Follow-Up From the Children's Toddler School Program*. *J POSIT BEHAV INTERV* 2010, **12**(4):245-253.

29. Bibby P, Eikeseth S, Martin NT, Mudford OC, Reeves D: *Progress and outcomes for
children with autism receiving parent-managed intensive interventions. *RES DEV DISABIL* 2001, **22**(6):425-447.

30. Clark ML, Barbaro J, Dissanayake C: *Continuity and Change in Cognition and Autism Severity from Toddlerhood to School Age*. *J AUTISM DEV DISORD* 2017, **47**(2):328-339.

31. Cohen H, Amerine-Dickens M, Smith T, Correspondence A, M. Amerine-Dickens ORMC, Email MCO: *Early intensive behavioral treatment: Replication of the UCLA model in a community setting*. 2006, **27**(2 SUPPL. 2):S145-S155.

32. Gabriels RL, Hill DE, Pierce RA, Rogers SJ, Wehner B: *Predictors of treatment outcome in young children with autism: a retrospective study*. *AUTISM* 2001, **5**(4):407-429.

33. Harris SL, Handleman JS: *Age and IQ at intake as predictors of placement for young children with autism: a four- to six-year follow-up*. *J AUTISM DEV DISORD* 2000, **30**(2):137-142.

34. Howard JS, Stanislaw H, Green G, Sparkman CR, Cohen HG: *Comparison of behavior analytic and eclectic early interventions for young children with autism after three years*. *RES DEV DISABIL* 2014, **35**(12):3326-3344.

35. Landa RJ, Kalb LG: *Long-term outcomes of toddlers with autism spectrum disorders exposed to short-term intervention*. *PEDIATRICS* 2012, **130** Suppl 2(Supplement 2):S186-S190.

36. Lovaas OI: *Behavioral treatment and normal educational and intellectual functioning in young autistic children*. *J Consult Clin Psychol* 1987, **55**(1):3-9.

37. McEachin JJ, Smith T, Lovaas OI: *Long-term outcome for children with autism who received early intensive behavioral treatment*. *Am J Ment Retard* 1993, **97**(4):359-372, 373-391.
38. Sallows GO, Graupner TD: **Intensive behavioral treatment for children with autism: four-year outcome and predictors.** *Am J Ment Retard* 2005, **110**(6):417-438.

39. Smith T, Groen AD, Wynn JW: **Randomized trial of intensive early intervention for children with pervasive developmental disorder.** *Am J Ment Retard* 2000, **105**(4):269-285.

40. Smith T, Klorman R, Mruzek DW: **Predicting Outcome of Community-Based Early Intensive Behavioral Intervention for Children with Autism.** *J Abnorm Child Psychol* 2015, **43**(7):1271-1282.

41. Vinen Z, Clark M, Paynter J, Dissaneyake C: **School Age Outcomes of Children with Autism Spectrum Disorder Who Received Community-Based Early Interventions.** *J Autism Dev Disord* 2018, **48**(5):1673-1683.

42. Weiss MJ, Delmolino L: **The relationship between early learning rates and treatment outcome for children with autism receiving intensive home-based applied behavior analysis.** *The Behavior Analyst Today* 2006, **7**(1):96-110.

43. Kovshoff H, Hastings RP, Remington B, Correspondence A, H. Kovshoff SOPU, Southampton SOBJ: **Two-year outcomes for children with autism after the cessation of early intensive behavioral intervention.** 2011, **35**(5):427-450.

44. Perry A, Koudys J, Prichard A, Ho H: **Follow-Up Study of Youth Who Received EIBI as Young Children.** 2019, **43**(2):181-201.

45. Virués-Ortega J, Correspondence A, J. Virués-Ortega CNDE, Carlos Iii SDMS, Com JC: **Applied behavior analytic intervention for autism in early childhood: Meta-analysis, meta-regression and dose-response meta-analysis of multiple outcomes.** 2010, **30**(4):387-399.

46. Maurice CE, Green GE, Luce SC: **Behavioral intervention for young children with...**
autism: A manual for parents and professionals.: Pro-ed; 1996.

47. Reichow B, Barton EE, Boyd BA, Hume K: Early intensive behavioral intervention (EIBI) for young children with autism spectrum disorders (ASD). COCHRANE DB SYST REV 2012(10).

48. Oono IP, Honey EJ, McConachie H: Parent-mediated early intervention for young children with autism spectrum disorders (ASD). Cochrane Database Syst Rev 2013(4):D9774.

49. Xu G, Strathearn L, Liu B, O’Brien M, Kopelman TG, Zhu J, Snetselaar LG, Bao W: Prevalence and Treatment Patterns of Autism Spectrum Disorder in the United States, 2016. JAMA PEDIATR 2019, 173(2):153-159.

50. Vivanti G, Kasari C, Green J, Mandell D, Maye M, Hudry K: Implementing and evaluating early intervention for children with autism: Where are the gaps and what should we do? AUTISM RES 2018, 11(1):16-23.

51. Lord C, Bishop S, Anderson D: Developmental trajectories as autism phenotypes. In: 2015-01-01 2015. Wiley Online Library; 2015:198-208.

52. Szatmari P, Georgiades S, Duku E, Bennett TA, Bryson S, Fombonne E, Mirenda P, Roberts W, Smith IM, Vaillancourt T: Developmental trajectories of symptom severity and adaptive functioning in an inception cohort of preschool children with autism spectrum disorder. JAMA PSYCHIATR 2015, 72(3):276-283.

53. Di Rezze B, Duku E, Szatmari P, Volden J, Georgiades S, Zwaigenbaum L, Smith IM, Vaillancourt T, Bennett TA, Elsabbagh M: Examining Trajectories of Daily Living Skills over the Preschool Years for Children with Autism Spectrum Disorder. J AUTISM DEV DISORD 2019, 49(11):4390-4399.

54. Smith LE, Maenner MJ, Seltzer MM: Developmental trajectories in adolescents and adults with autism: The case of daily living skills. Journal of the American
Academy of Child & Adolescent Psychiatry 2012, 51(6):622-631.

55. Strain PS: **Four-Year Follow-Up of Children in the LEAP Randomized Trial:**

**Some Planned and Accidental Findings.** *TOP EARLY CHILD SPEC* 2017, 37(2):121-126.

**Figures**

Flowchart of the retrieval and selection of references. ASD, autism spectrum disorder; CTM, comprehensive treatment models; IQ, intelligence quotient; VABS, Vineland Adaptive Behavioral Scales.
Effect sizes (gc) for IQ, language and symptom outcomes in children with ASD. Hedges’ g effect sizes represented in black and confidence intervals are reported. Random effects models were used on all outcomes, and the studies were rank-ordered by quality rating.

ASD, autism spectrum disorder; CI, confidence interval; EIBI, early intensive behavioral intervention; ES, effect sizes; ESDM, Early Start Denver Model; IQ, intelligence quotient.
Effect sizes (gc) for adaptive functioning in children with ASD. Hedges’ g effect sizes represented in black and confidence intervals are reported. Random effects models were used on all outcomes, and the studies were rank-ordered by quality rating. CI, confidence interval; EIBI, early intensive behavioral intervention; ES, effect sizes; ESDM, Early Start Denver Model; VABS, Vineland Adaptive Behavioral Scales.
|                        | Sallows (2005)* | Howard (2014) | Cohen (2006) | Smith (2000)* | Overall |
|------------------------|-----------------|---------------|--------------|---------------|---------|
| Receptive language     | 20.95           | -0.30         | -1.13        | 0.53          |         |
|                        |                 | 26.35         | 0.98         | 0.30, 1.66    |         |
|                        |                 | 29.24         | 0.40         | -0.22, 1.01   |         |
|                        |                 | 23.46         | 0.48         | -0.28, 1.23   |         |
|                        |                 | 100.00        | 0.42         | -0.06, 0.91   |         |

Heterogeneity: $I^2$-squared=56.1%, Publication bias: $P=0.543$

|                        | Sallows (2005)* | Howard (2014) | Cohen (2006) | Smith (2000)* | Overall |
|------------------------|-----------------|---------------|--------------|---------------|---------|
| VABS composite        | 15.50           | 18.51         | 23.75        | 18.29         |         |
|                        | 0.10            | 1.10          | 0.68         | 0.11          |         |
|                        | -0.73, 0.92     | 0.36, 1.84    | 0.06, 1.31   | -0.64, 0.85   |         |
|                        |                 |               |              |               |         |
|                        |                 |               |              |               |         |
|                        |                 |               |              |               |         |
|                        |                 |               |              |               |         |

Heterogeneity: $I^2$-squared=45.5%, Publication bias: $P=0.451$

|                        | Sallows (2005)* | Howard (2014) | Cohen (2006) | Smith (2000)* | Overall |
|------------------------|-----------------|---------------|--------------|---------------|---------|
| VABS communication    | 15.22           | 19.21         | 23.28        | 18.06         |         |
|                        | -0.25           | 0.78          | 0.74         | 0.28          |         |
|                        | -1.08, 0.57     | 0.06, 1.50    | 0.10, 1.37   | -0.47, 1.02   |         |
|                        |                 |               |              |               |         |
|                        |                 |               |              |               |         |
|                        |                 |               |              |               |         |

Heterogeneity: $I^2$-squared=24.2%, Publication bias: $P=0.739$

|                        | Sallows (2005)* | Howard (2014) | Cohen (2006) | Smith (2000)* | Overall |
|------------------------|-----------------|---------------|--------------|---------------|---------|
| VABS social           | 15.14           | 18.46         | 24.15        | 18.11         |         |
|                        | 0.26            | 0.98          | 0.57         | -0.12         |         |
|                        | -0.57, 1.08     | 0.24, 1.71    | -0.05, 1.19  | -0.86, 0.63   |         |
|                        |                 |               |              |               |         |
|                        |                 |               |              |               |         |
|                        |                 |               |              |               |         |

Heterogeneity: $I^2$-squared=21.0%, Publication bias: $P=0.412$

|                        | Sallows (2005)* | Cohen (2006) | Smith (2000)* | Kovshoff (2011) | Overall |
|------------------------|-----------------|--------------|---------------|-----------------|---------|
| VABS daily living skills | 17.29          | 31.30        | 21.32         | 30.09           |         |
|                        | 0.09            | 0.13         | -0.03         | 0.45            |         |
|                        | -0.73, 0.92     | -0.49, 0.74  | -0.77, 0.71   | -0.18, 1.07    |         |
|                        |                 |               |               |                 |         |
|                        |                 |               |               |                 |         |
|                        |                 |               |               |                 |         |

Heterogeneity: $I^2$-squared=20.8%, Publication bias: $P=0.891$

|                        | Sallows (2005)* | Cohen (2006) | Smith (2000)* | Kovshoff (2011) | Overall |
|------------------------|-----------------|--------------|---------------|-----------------|---------|
| Figure 4              |                 |               |               |                 |         |
SMD (gd) for multiple outcomes of EIBI in children with ASD. Notes: comparison type * EIBI therapist vs. EIBI parents; † EIBI vs. EIBI minimal intensity. CI, confidence interval; ES, effect sizes; IQ, intelligence quotient; SMD, standardized mean difference.

Supplementary Files
This is a list of supplementary files associated with this preprint. Click to download.
Additional files_Table S1-S3.docx
Additional files_PRISMA 2009 checklist.doc