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Research Paper

A developmental and sequenced one-to-one educational intervention (DS1-EI) for autism spectrum disorder and intellectual disability: A three-year randomized, single-blind controlled trial

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ABSTRACT

Background: Children with autism spectrum disorder (ASD) and intellectual disability (ID) are an under-studied population whose school inclusion is challenging.

Methods: We assessed the effects of "Developmental and Sequenced one-to-one Educational Intervention" (DS1-EI), a ten-hour-per-week adapted instruction programme for five- to nine-year-old children with ASD and ID treated in outpatient health care institutions. A single-blind multisite randomized controlled trial was conducted to compare DS1-EI given for three years with treatment as usual (TAU)(trial registration numbers: ANSM130282B-31 (April 16, 2013) and ACTRN12616000592448). The primary outcome was the change in the psycho-educational profile (PEP). Secondary variables included the Childhood Autism Rating Scale (CARS), Autism Diagnostic Interview-Revised (ADI-R), Vineland Adaptive Behaviour Scale-II (VABS-II), Children's Global Assessment Scale (CGAS) and annual assessment of educational achievement. Statistical analyses used linear mixed models.

Findings: Seventy-two participants with severe ASD and ID were recruited. Intention-to-treat and per-protocol analyses showed no significant group*time interaction for the PEP, CARS, ADI-R, VABS-II and CGAS but a significant effect for educational achievement with a better improvement in the DS1-EI group. At the 36-month time point, more DS1-EI children were included in mainstream classrooms. Additional analyses using multivariate models taking into account moderating variables at the baseline (e.g., Developmental Quotient) confirmed that DS1-EI had a significant effect on educational outcomes.

Interpretation: DS1-EI did not improve communication or social skills in children with ASD and ID compared with TAU. However, DS1-EI enhanced school skills in four domains (language, mathematics, inter modality, and school autonomy) favouring inclusion in mainstream classrooms more than TAU. Providing such adapted instruction is feasible and should be encouraged.

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1. Introduction

Autism spectrum disorders (ASDs) are a group of neurodevelopmental disorders showing symptoms that manifest in early childhood. They are characterized by persistent deficits in social communication and interaction across multiple contexts associated with restricted, repetitive patterns of behaviours, interests or activities [1]. The symptoms cause clinically significant impairments in

Research in context

Evidence before this study

Evidence based treatment approaches in autism have mainly assessed patients without intellectual disability (ID), medical condition and socioeconomic adversity. However, the same treatment principles are applied to children with ID. Also, school inclusion is recommended for both education and socialisation.

Added value of this study

The current study reports a 3-year single-blind multisite randomized controlled trial assessing an instruction programme for children with autism implemented in day-care institutions in the French context of free access to care. It allowed including patients with autism and ID, and eventually comorbid medical conditions and low socioeconomic backgrounds. At end-point the programme was better than treatment as usual in terms of educational variables.

Implications of all the available evidence

Providing such adapted instruction is feasible and should be encouraged even in children with autism and comorbidities. We believe that cultural adaptation may be warranted to assess the program outside the French context.

social, occupational or other important areas of functioning. Early interventions are based on educational, behavioural and developmental approaches. The main ones are early intensive behavioural intervention (EIBI) [2], the Early Start Denver Model (ESDM) [3], the Treatment and Education of Autistic and Communication Handicapped Children (TEACCH) program [4], the exchange and development therapy [5] and the Joint Attention Symbolic Play Engagement and Regulation (JASPER)[6]. Care for children with ASD should also include parent-mediated interventions (e.g., parent-mediated communication-focused treatment-PACT) [7,8], educational interventions, specific therapies (e.g., speech therapy, occupational therapy, psychotherapy), and adapted instruction [9]. However, there is insufficient evidence to determine which specific interventions are the most effective treatments for children with ASDs [10]. Also, naturalistic developmental behavioural interventions (NDBI) could be the most promising according to a recent therapeutic review taking into account study quality indicators [11].

What treatments are offered to children with ASD depends on the health system, the financial support available, and the school system's openness to accommodating children with special educational needs [12]. In countries with significant constraints on the health care system (e.g., the US), treatment is offered within the educational system. In contrast, in countries with free access to care (e.g., most European countries), most therapies, including some aspects of education, are provided within the health care system. In the latter, there is a greater risk that children with ASD will be excluded from mainstream schools. This is the case in France, where as the number of separate institutions dedicated to serving children with ASD and ID grew in the 1970s, and integration into mainstream schools was difficult, especially when moderate to severe ID was involved [13]. In a large survey conducted in Europe, factors mediating treatment access included healthcare systems, family socio-economic background, the children's age, and the time passed since diagnosis rather than the children's characteristics [14].

Currently, in France, 88% of children with ASD attend school. More severe adaptive and cognitive deficits are associated with less or no

schooling [15]. In addition, school-age children with ASD and moderate to severe ID usually do not receive educational programming services in mainstream classrooms, as is the case in the US, but receive institutional care in specialized outpatient health care organizations (e.g., day-care hospitals and medical-educational institutes). Because few of these include formalized instruction, it is important to determine whether more educational interventions and programming can be incorporated into daily practice, especially in the understudied population of children with ASD and moderate to severe ID.

There are very few studies assessing the impact of school-based interventions for children with ASD, and most of them focus on one aspect of ASD symptoms [16] (e.g., stereotypies, socialization with peers, functional leisure engagement). Lopata et al. [17] conducted a comprehensive school-based intervention for children with ASD without ID aged 6 to 12 years. The programme significantly improved emotion recognition skills, ASD symptoms, social skills, and social-communication skills but not academic achievement. We found only one study [18] assessing the benefit of an intervention (the TEACCH programme) targeting children with ASD and severe ID implemented at home and at mainstream schools. The effectiveness of TEACCH appeared to be confirmed, showing positive outcomes in the natural setting and revealing its inclusive value.

Here, we assessed the effects of "Developmental and Sequenced one-to-one Educational Intervention" (DS1-EI), a ten-hour-per-week adapted instruction programme for children with ASD and ID. To do so, we conducted a prospective single-blind randomized controlled trial taking place in the framework of overall institutional care. This school-based intervention includes elements borrowed from behavioural and developmental approaches (such as ABA, ESDM and TEACCH), but DS1-EI stands out for its use of pedagogy to foster interpersonal relationships [19]. We first evaluated the results after 24 months of the DS1-EI interventions. Patients in the DS1-EI group did not improve better than patients in the treatment as usual (TAU) group [20]. The aim of the current study was to evaluate the benefits of DS1-EI intervention on verbal communication, non-verbal communication, social skills and educational achievements at 36 months, the end-point of the study.

2. Methods

2.1. Ethics

The study was allowed by the French national health regulatory authority (*Agence nationale de sécurité du médicament et des produits de santé*-ANSM) and was registered under ANSM 130282B-31 (April 16, 2013). The study was approved by the local ethics committee (*Comité de Protection des Personnes*) of the Saint-Antoine University Hospital on May 7, 2013, and was also registered on the Australian New Zealand Clinical Trial Registry under trial registration number ACTRN12616000592448 (May 6, 2016). Potential participants received verbal information about the study adapted to their level of comprehension, and their legal representatives were provided verbal and written information about the trial. All parents gave written informed consent prior to inclusion.

2.2. Subject recruitment

Participants were recruited from 11 French 'full time' outpatient health care institutions providing 30 to 35 h per week of treatment for children with co-occurring ASD and ID. To obtain a sample of French children representative of the children treated in day-care hospitals and medico-educational institutes, the study sites were located throughout France, including one site in an overseas territory, Guadeloupe. There were six day-care hospitals and five medico-educational institutes. Inclusion criteria were a diagnosis of ASD confirmed by clinical assessment based on the International

Classification of Diseases, 10th edition (ICD-10) and the Autism Diagnostic Interview Revised (ADI-R)[21]; age between five and nine years; communication developmental age of 24 months or fewer or delayed language of three years as evaluated on the Vineland Adaptive Behaviour Scale, Second Edition (VABS-II)[22]; and determination by French education regulators that it is not possible to include the child in a mainstream or special education classroom. Children with other medical comorbidities, stabilized or not, were not excluded from the study. Exclusion criteria were only the absence of parental consent or a planned change of institution within the duration of the study.

The intellectual quotient (IQ) was assessed for all participants based on the Kaufman Assessment Battery for Children, Second Edition (KABC-II) [23]. When there was a flor effect for measurement, the VABS-II was used to obtain a developmental quotient (DQ).

2.3. Randomisation

We created dyads of participants matched by IQ or DQ (and when possible by age and sex to minimize bias) in each institution. Randomization for group allocation was performed by drawing lots in each dyad and was stratified on the implementation study site. Randomization was performed by the methodological coordinating team at the Salpêtrière Hospital independent of the institutions. Each site included six to eight participants distributed in the TAU group, and the DS1-EI group consisted of three to four children each.

2.4. Design of the study

The study was a randomized, single-blind multicentric controlled trial. The protocol started sequentially in April 2013, when experimental classes were set up in each institution. The study was conducted for 36 months at each site. The children in the control group (TAU group) received the usual instruction and institutional care (e.g., speech therapy, social-skills group activities, occupational therapy) for 30 to 35 h per week. The experimental group (DS1-EI group) was exposed to an intensive (ten hours per week) structured one-to-one pedagogic workshop during which children received individual, sequential and developmental instruction. They continued to receive the usual treatments for the remaining 20−25 h of programming. In summary, patients in the control group received 30 to 35 h per week of TAU that included few hours of school with no specific instruction, whereas patients in the experimental group received 20 to 25 h of TAU and 10 h of DS1-EI.

2.5. DS1-EI intervention

The DS1-EI principles are detailed in Tanet et al. [19]. A brief overview is offered in supplemental materials. The treatment protocol was adapted for school implementation by designing it using an educational agenda based on French Ministry for National Education's objectives and following principles of the Handiscol plan [24]. The intervention is based on regular assessments, updating objectives, encouraging spontaneous communication, promoting skills through play with peers, supporting positive behaviours, providing supervision, capitalizing on teachers' unique skills, and providing developmental (Vygotsky's zone of proximal development theory)[25] and sequenced learning (meaning that the teacher changes the learning activities every 10−15 min to maintain the child's attention in the context of an anticipated time agenda).

2.6. Outcome measures

The primary outcome measure was change in the Psychoeducational Profile, Third Edition (PEP-3). The PEP-3, which aimed to assess changes in verbal communication, non-verbal communication and

social skills, is a standardized play-based assessment made up of ten subtests: six measure developmental abilities (verbal and preverbal cognition, expressive language, receptive language, fine motor skills, gross motor skills and visual-motor imitation), and four measure maladaptive behaviours (affective expression, social reciprocity, characteristic motor behaviours, and characteristic verbal behaviours). From these subtests, the PEP-3 produces three composite scores (PEP-communication, PEP-motor and PEP-maladaptive behaviours) and a total developmental quotient (DQ) [26].

The secondary outcome measures included the Childhood Autism Rating Scale (CARS), ADI-R, the VABS-II, Children's Global Assessment Scale (CGAS) and annual educational achievement. The CARS, which was used to monitor the intensity of ASD manifestations, is a fifteen-item behavioural rating scale used in diagnosing children with autism and determining symptom severity [27]. The ADI-R is a standardized, semi-structured interview with parents, focusing on three areas of development: social interaction (ADI-interaction), communication and language (ADI-communication), and restricted and repetitive behaviours (ADI-stereotypies) [21]. The VABS-II is completed during an interview with a caregiver and assesses the ability of a child to perform the activities of daily living required for personal and social autonomy. The scale measures adaptive behaviour in four domains: communication (VABS-communication), daily livings (VABS-autonomy), socialization (VABS-social), and motor skills (VABS-motricity). The subscale scores are totalled to obtain a development quotient (DQ) [22]. The CGAS provides a global measure of the level of functioning in children and adolescents. Based on the clinician's assessment of a range of aspects related to a child's psychological and social functioning, the child is given a single global rating between 1 and 100, corresponding to one of the ten degrees of impairment from "needs constant supervision" (1−10) to "superior functioning" (91−100) [28]. Educational achievement was assessed on French national expectations for pre-schoolers (http://eduscol.education.fr) according to the developmental age of participants. Educational achievement evaluates 13 areas belonging to four domains: language (oral language, written language, communication, pre-writing skills), mathematics (numeracy, problem solving), inter modality (writing/drawing activities and listening, musical activities), and school autonomy (discovering the world, motor activities, social skills and perception).

A single-blind procedure was used for clinical assessments (CARS and PEP-3), but this was not possible for measures requiring a two-week observation of participants (educational achievement and CGAS) or a parental interview (ADI-R and VABS-II). The CARS, PEP-3 and ADI-R were assessed at the baseline, 18 months and 36 months, whereas educational achievement, the VABS-II and the CGAS were assessed annually (at the baseline, 12 months, 24 months and 36 months). Finally, at the end of the study, based on a preliminary report at 24 months that indicated several children were about to start attending a mainstream school, we also asked regarding each child whether he or she was scheduled to be included in an adapted school setting inside an ordinary school.

2.7. Statistical analysis

Statistical analyses were performed using R Software, version 3.3.1 (R Foundation for Statistical Computing) [29], by resorting to two-tailed tests with a level of significance fixed at 5%.

The data were subjected to intention to treat (ITT) and per-protocol (PP) analyses. The populations of these two types of analyses were defined from all randomized patients considering the deviations presented by each of them. Total deviations included the absence of randomization and refusal of group allocation. Patients with total deviation were excluded from all analyses. Major deviations corresponded to dropping out before the end of the protocol. Minor deviations resulted from a negligible change in the

intervention or a slight delay in the test completion compared to what was planned. The population for ITT analyses included patients with no deviation, minor deviation, and major deviation. The population for PP analyses excluded patients with major deviation. Missing data were assessed for each variable and considered using linear mixed-effects models.

As the data involved repeated measures, the evolution of primary and secondary variables across time was analysed using linear mixed models (lme4 package). Each outcome variable was studied separately for an explanation by the model. Variables were explained by group exposure, time, (group*time) interaction, and DQ score at baseline, subject and centre (subject and centre were used as random intercepts, with the subject nested within centre). This should allow individual heterogeneity, site heterogeneity, variable inclusion scores, and DS1-EI-specific changes within the same statistical regression to be considered. The goal of the group*time interaction assessment was to evaluate whether the clinical evolution differed between groups. For each outcome variable, estimated group*time interaction effect, the corresponding 95% BCa bootstrapped confidence interval (95% CI) and percentile bootstrapped p value were reported (boot package, R = 10,000 replications).

To educational achievement over time, participants were evaluated on several items over two levels of progression (http://eduscol.education.fr). Each level's items were grouped into 13 subdomains. First, subdomain scores were defined as the mean of their item scores. This process was performed for both levels. Second, each subdomain score of the first level was averaged with its respective subdomain score of the second level. The goal was to obtain a unique score per subdomain for each subject and at a given time point. Two subdomains only belonged to one level of progression, so their score was used as the final score. Thirteen scores were obtained at the end of these steps for each subdomain: oral language, written language, communication, pre-writing skills, numeracy, problem solving, writing/drawing activities and listening, musical activities, discovering the world, motor activities, social skills and perception. Evolution over time was modelled using linear mixed effects models as mentioned before. One model was run per subdomain, the variance of which was explained by time, group and group*time interaction. The subject effect was used as a random intercept to account for repeated measures over time.

As the outcome could be influenced by the initial characteristics of the two groups, including covariates showing an initial imbalance in the multivariate model was planned to correct any bias, but none was required in our model.

2.8. Additional statistical analysis

Since autism is a heterogeneous disorder, we also performed post hoc analysis to assess experimental group effects that were significant taking into account variables known to moderate clinical outcome. To limit the number of variables to be explored, we used the VABS-ABC composite because it has been recently shown that a given numerical change in the VABS-ABC is more likely to be clinically meaningful than a numerically identical change that is limited to any given VABS-II domain [30]. These variables included ADI-R total score, VABS-ABC at baseline, the existence of somatic comorbidity, parental education, DQ at baseline, gender, receiving speech therapy at baseline, study site, receiving a drug, and treatment group. Given the sample size, we only kept in the multivariate models the variables that were associated with outcome at a $p < .2$ using univariate analyses. Then we performed an ordinal logistic regression to explain the educational outcome (mainstream classroom vs. no mainstream classroom at 3 years).

2.9. Role of funding

The funding sources did not intervene in the design, collection, interpretation of the data. They only supported staff needed to conduct the clinical study, the data monitoring, and the statistical analyses.

3. Results

3.1. Definition of ITT and PP samples

The flowchart is presented in Fig. 1. Amongst the 75 screened children, three did not enter the study. In one case, the parents refused group allocation (DS1-EI group), which led to the exclusion of the child with whom he formed a dyad. The third child did not enter the study because he was not part of a dyad. The remaining 72 participants were randomized equally with 36 in each group and composed the population for ITT analyses. Four subjects from the TAU group (11.1%) did not complete the study: they dropped out because they left the institution. Five subjects from the DS1-EI group (13.9%) did not complete the study: one subject's parent withdrew consent for the study, two had behavioural impairments that prevented participation, and two subjects left their institutions. These 9 subjects were excluded from the PP analyses. The protocol attrition was good, as evidenced by the low number of study outings before the end of the protocol.

3.2. Participants

The participants' baseline characteristics are presented in Table 1. There was no significant difference between groups. Approximately 15% were female, and the mean age was approximately seven years old. Many children heard a foreign language at home or were bilingual, as their parents were migrants (44.4%). Parental education level was rather low. Children received the same amount of speech therapy, psychotherapy and occupational therapy. Fifteen percent received psychotropic medication. Children had severe autism as evidenced by an average CARS score greater than 40 and a moderate to severe ID with a VABS developmental age in communication or socialization of approximately 15 months for a mean chronological age of 84 months. Fifteen patients had medical comorbidities: six in the DS1-EI group (very preterm, Rubinstein-Taybi syndrome, Down syndrome, metabolic syndromes, early puberty, pigmentary retinitis) and nine in the TAU group (very preterm (N = 3), neonatal hypoxaemia, deletion of HNF1-B and TCF2 genes, association of Williams-Beuren syndrome and hemiplegia, Fragile X syndrome, seizures, cerebral malformation). As expected, we found a significant difference in terms of the duration of schooling, reflecting the study protocol: in the TAU group, children had very little schooling and were receiving an average of 3 h per week, compared to 10 h in the DS1-EI group.

3.3. Outcomes at 36 months

The ITT results are presented in Table 2. Group*time interaction analyses did not show any differential evolution between the two groups for the CARS (p = .465) and the three composite PEP-3 scores (PEP-communication p=.929, PEP-motor p=.150, PEP-maladaptive behaviours p=.745). There was no significant difference in the evolution of groups regarding the secondary clinical outcome measures. However, participants in both groups significantly improved over time for the CARS (decrease of 4.68 points) and for the PEP-3 composite scores (PEP-communication increase of 7.56 points, PEP-motor increase of 5.76 points, and PEP-maladaptive behaviour increase of 3.24 points). Likewise, there was a significant improvement over the 36 months in the CGAS (increase of 9.72 points) and in the VABS developmental age in the four domains (VABS-communication increase of 12.24 months, VABS-autonomy increase of 16.92 months, VABS-social increase of 14.76 months, and VABS-motricity increase of 14.0 months). Delta scores (baseline value − 36-month value) and Cohen's d effect sizes are given in Table 3.
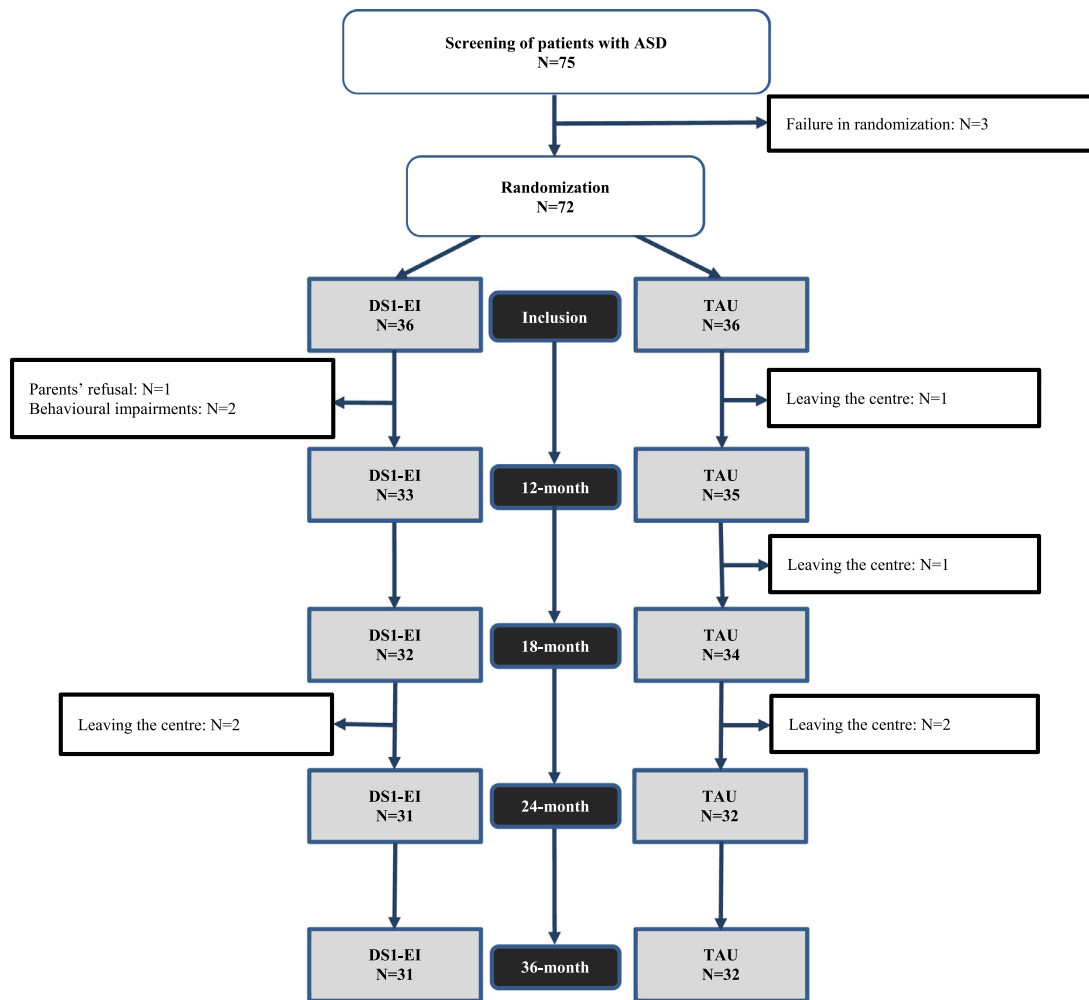
Fig. 1. Flowchart.

In contrast, educational achievement showed a significant group*-time interaction in favour of the DS1-EI group. All items significantly improved more in the DS1-EI group than in the TAU group (see Table 2). Additionally, at the end of the study, there was a project of school orientation with a mainstream classroom for 12 (33%) participants in the DS1-EI group versus 1 (2.7%) participant in the TAU group. Likewise, there was a project of instruction internal to the institution for 21 (58%) and 27 (75%) of the participants in the DS1-EI and TAU groups, respectively. Two (5.6%) children in the DS1-EI group and 6 (17%) children in the TAU group had no instruction at all (Fig. 2). Again, the DS1-EI group participants were significantly more likely to be orientated in mainstream classrooms than the TAU group participants (Fisher exact test, p-value=0.001).

The results of the PP analyses were consistent with those of the ITT analyses and are presented in supplemental materials. There was a trend towards significance of the group*time interaction for VABS-communication (p=.085) with a group*time estimate of 0.12, meaning that VABS-communication tended to improve by 4.3 months more in the DS1-EI group than in the TAU group over the 36 months of the study (Fig. 3).

3.4. Additional analyses

Since autism is a heterogeneous disorder, we also performed additional analyses to assess whether some variables known to moderate clinical outcome (e.g. DQ; socio-economic background; access to oral language) interfered with our most significant results. In other words, we assessed whether the DS1-EI effects on orientation in mainstream classrooms changed when variables known to moderate clinical outcome were considered in the same multivariate model. Given our limited sample size and to limit the number of variables included in the multivariate model, we first performed univariate analyses to explore whether the following variables at baseline were associated to educational outcome with a p<.2: ADI-R scores at baseline, the existence of a somatic comorbidity, parental education, DQ at baseline, gender, receiving speech therapy at baseline, study site, receiving a drug. We found that 3 variables should be included in the multivariate model: DQ at baseline, receiving a drug and ADI-R social interaction score at baseline. Then, we performed a multivariate model (ordinal logistic regression) to predict orientation in mainstream classroom at end-point. We found that orientation in mainstream classrooms at 3-year FU was predicted by DQ at the baseline (OR=1.18 [95%CI: 1.09;1.29]p<.001), receiving a drug (OR=0.1 [95%CI: 0.01;0.75]p<.027), and receiving DS1-EI (OR=8.19 [95%CI: 1.86;53.77], p< .014) (see supplemental materials). Despite the influence of DQ and receiving a drug at baseline on outcome, receiving DS1-EI still predicted with a large OR orientation in mainstream classrooms at 3-year FU.

4. Discussion

We examined the efficacy of the DS1-EI intervention on communication, social skills, and educational achievement for children with ASD and moderate/severe ID treated within French specialized health

Table 1
Sociodemographic and clinical characteristics at baseline.

	DS1-EI group (N = 36)	TAU group (N = 36)	Test, p
Socio-demographics			
Sex: Female/Male	5 (13·9%)/31 (86·1%)	6 (16·7%)/30 (83·3%)	Chi2, p = 1
Age (in months)	82·4 (19·1)	87 (19·5)	W = 546·5, p=·26
Foreign language spoken at home (yes/no)	14 (38·9%)/22 (61·1%)	18 (50%)/18 (50%)	Chi2, p= ·48
Associated disorder (yes/no)	6 (16·7%)/30 (83·3%)	9 (25·0%)/27 (75·0%)	Chi2, p=·56
Psychotropic medication (yes/no)	5 (13·9%)/31 (86·1%)	6 (16·7%)/30 (83·3%)	Chi2, p = 1
Speech therapy*	0·8 (0·8)	0·8 (0·7)	W = 612, p=·83
Psychotherapy*	0·4 (0·6)	0·5 (0·7)	W = 619, p= ·7
Occupational therapy*	0·7 (0·8)	1 (0·8)	W = 520, p= ·12
Composite score of family support	2·2 (0·8)	2·1 (0·8)	W = 678·5, p=·72
Composite parental education level	4·6 (1)	4·6 (1·2)	W = 362·5, p=·99
Clinical characteristics			
Developmental quotient	0·3 (0·1)	0·3 (0·1)	W = 692, p= ·48
CARS	40·6 (7·1)	40·2 (7·1)	W = 681·5, p=·71
ADI-interaction	20·8 (5·8)	20·1 (5·8)	W = 667, p=·67
ADI-communication	11·8 (4·1)	10·8 (3·2)	W = 735·5, p=·22
ADI-stereotypies	6·4 (2·7)	5·8 (3·2)	W = 693, p=·47
PEP-communication	17·6 (7·1)	18·4 (7·9)	W = 600·5, p=·6
PEP-motor	24·6 (8)	25·7 (7)	W = 605, p=·63
PEP-maladaptive behaviours	9·7 (4·6)	9·6 (4·5)	W = 672·5, p=·79
VABS-communication (age)	15 (7·7)	15 (5·8)	W = 608·5, p=·66
VABS-autonomy (age)	28·6 (10·6)	27·9 (10·5)	W = 682, p= ·71
VABS-social (age)	15·2 (8·2)	14·6 (9)	W = 704·5, p=·53
VABS-motricity (age)	33·3 (10·1)	32 (9·8)	W = 697·5, p=·58
CGAS	25·8 (12)	24·8 (11)	W = 696·5, p=·59

DS1-EI: Developmental and Sequenced One-to-One Educational Intervention; TAU: Treatment as usual; ADI-R: Autism Diagnostic Interview-Revised; PEP: PsychoEducational Profile; VABS: Vineland Adaptive Behaviour Scale; CGAS: Clinical Global Assessment Score.

* number of sessions per week per participants (mean).

care institutions compared to TAU. There was no significant differential evolution between the two groups for the clinical primary and secondary outcome variables, except there was a trend towards significance of the group*time interaction for VABS-communication in favour of the DS1-EI group in the PP analyses (see supplemental materials). However, educational achievement was significantly improved in the DS1-EI group in both the ITT and the PP analyses, which we believe is linked to intervention exposure, as school skills are directly targeted by the programme. This means that (1) DS1-EI implementation was feasible despite the children's low IQ, which

Table 2
Group*time interaction and time effect (Intention-to-treat analyses).

	group*time estimate	[IC95%]	p	time estimate	[IC95%]	P
CARS	−0·03	[−0·12; 0·05]	0·465	−0·13	[−0·17; −0·09]	< 0·001
ADI-interaction	0·01	[−0·07; 0·09]	0·796	−0·15	[−0·19; −0·11]	< 0·001
ADI-communication	−0·04	[−0·11; 0·03]	0·244	−0·03	[−0·06; 0·01]	0·153
ADI-stereotypies	−0·01	[−0·05; 0·03]	0·607	0·00	[−0·02; 0·02]	0·678
PEP-motor	0·05	[−0·02; 0·12]	0·150	0·16	[0·12; 0·19]	< 0·001
PEP-communication	0·00	[−0·08; 0·09]	0·929	0·20	[0·16; 0·24]	< 0·001
PEP-maladaptive behaviours	0·01	[−0·03; 0·05]	0·745	0·09	[0·07; 0·11]	< 0·001
VABS-communication	0·10	[−0·03; 0·23]	0·134	0·33	[0·26; 0·39]	< 0·001
VABS-autonomy	0·06	[−0·08; 0·20]	0·426	0·46	[0·39; 0·53]	< 0·001
VABS-social	0·03	[−0·14; 0·19]	0·725	0·40	[0·32; 0·49]	< 0·001
VABS-motricity	−0·03	[−0·19; 0·13]	0·733	0·40	[0·32; 0·47]	< 0·001
CGAS	0·03	[−0·08; 0·13]	0·622	0·28	[0·22; 0·33]	< 0·001
School assessment language domain						
Oral language	0·01	[0; 0·01]	0·001	0·02	[0·02; 0·02]	< 0·001
Written language	0·01	[0; 0·01]	0·006	0·02	[0·02; 0·02]	< 0·001
Communication	0·01	[0·01; 0·02]	<0·001	0·02	[0·02; 0·02]	< 0·001
Pre-writing skills	0·01	[0; 0·02]	0·001	0·01	[0·01; 0·01]	< 0·001
School assessment mathematical domain						
Numeracy	0·01	[0; 0·01]	0·013	0·02	[0·01; 0·02]	< 0·001
Problem solving	0·02	[0·01; 0·02]	< 0·001	0·02	[0·02; 0·02]	< 0·001
School assessment intermodality						
Writing/drawing and listening	0·01	[0; 0·01]	0·002	0·02	[0·02; 0·02]	< 0·001
Musical activities	0·01	[0; 0·01]	0·01	0·02	[0·02; 0·02]	< 0·001
School assessment autonomy						
Discovering the world	0·01	[0; 0·02]	0·01	0·02	[0·01; 0·02]	< 0·001
Drawing activities	0·01	[0·01; 0·02]	< 0·001	0·02	[0·02; 0·02]	< 0·001
Motor activities	0·01	[0·01; 0·02]	< 0·001	0·02	[0·02; 0·02]	< 0·001
Social skills	0·01	[0; 0·02]	< 0·001	0·02	[0·02; 0·03]	< 0·001
Perception	0·01	[0; 0·02]	0·027	0·03	[0·02; 0·03]	< 0·001

ADI-R: Autism Diagnostic Interview-Revised; PEP: PsychoEducational Profile; VABS: Vineland Adaptive Behaviour Scale; CARS: Childhood Autism Rating Scale; CGAS: Clinical Global Assessment Score.
Positive estimates mean that developmental and sequenced one-to-one educational intervention is superior to treatment as usual.

Table 3
Variation and effect sizes over time in the DS1-EI and TAU groups (intention-to-treat analyses).

	DS1-EI group (N = 36)		TAU group (N = 36)	
	Delta	Cohen's d EF	Delta	Cohen's d EF
CARS	−5·38	−0·86	−3·58	−0·64
ADI-interaction	−5·45	−0·95	−5·83	−0·75
ADI-communication	−1·74	−0·37	−0·20	0·07
ADI-stereotypies	−0·45	−0·18	0·07	0·04
PEP-motor	6·77	0·97	4·68	0·59
PEP-communication	7·54	0·86	7·02	0·61
PEP-maladaptive behaviours	3·54	0·84	3·23	0·63
VABS-communication	14·77	1·02	9·52	0·75
VABS-autonomy	18·73	1·26	14·52	0·96
VABS-social	16·97	0·93	13·52	0·79
VABS-motricity	13·87	1·08	14·12	0·93
CGAS	10·36	1·14	9·60	0·99

Delta = baseline value − 36-month value; EF = effect size.

made their instruction harder: only 2 of the 36 DS1-EI group participants were not able to attend the class workshop because of behavioural impairment; (2) the implementation of the DS1-EI did not negatively impact clinical variables despite lowering other TAU proposals during the 20 h or so of TAU remaining. The acceptability was excellent, with a low proportion of dropouts (12.5%) during the 3-year duration of the study. All institutions continued the DS1-EI workshop after the end of the study. In addition, at the end of the study, DS1-EI group participants were more likely to be included in mainstream classrooms than TAU group participants. One may wonder if this was directly linked to improvement of school skills acquired though DS1-EI or to the observation that the child can act as a pupil and access learning. The findings of this study suggest that DS1-EI is an effective intervention for children with ASD and ID who are served within French day-care hospitals and medico-educational institutes. Additional analyses taking into account moderator variables at baseline confirmed the results since in the multivariate model, DS1-EI predicted orientations in the mainstream classroom at the end-point conclusion. Given our initial power hypothesis ($N = 80$, $d = 0.6$, p fixed at 0.05), we calculated the power on our real data for the significant results. For the multiple linear regressions on school assessment domains, we found that the study was correctly sized to detect effect sizes $f^2=0.11$. For the school orientation in a mainstream classroom, we calculated the power for a Chi squared test as an approximation of the Fisher's exact test. We found that the study was able to detect with a 80% power a minimal effect size d of 0.39.

This study brings interesting results for clinical practice, as we demonstrate that increasing the instruction time for patients with ASD and moderate to severe ID not only is possible through an adapted setting such as DS1-EI but also improves school abilities without impairing social and communication development and progress within the context of 'full time' outpatient health care institutions. This adapted school setting combined with institutional care seems to allow gains in socio-communicative skills joined with gains in learning skills. Moreover, it may allow some children to re-join special classrooms inside ordinary schools, which is a request by many parents in France and other countries [31]. This school inclusion is an interesting way to promote their socialization with peers.

The cooccurrence of ASD and ID is frequent and carries a poor prognosis. Children with these two conditions are often educated in kindergarten but only to a limited extent thereafter, as ASD management programmes rarely target school-aged children [31]. This is also the case in France, where 88% of children with ASD attend school but where children with both ASD and ID are less likely to attend school [15]. Additionally, the sample recruited here was notable for a high proportion of children of migrants, of low socio-economic backgrounds and of families with at least one significant morbidity. All these factors contribute to the overall severity of the sample, as it has been shown that ASD prognosis is dependant on family quality/stability [32] and that access to care in ASD is associated with higher parental educational level [14]. Many health agencies recommend conducting interventions at school, as they offer numerous benefits [33]. First, it is a simple way to increase the duration of specific interventions for children with ASD, including dual care from which they benefit greatly [34]. Intervention also allows the situations of communication and socialization both with peers and adults to be multiplied. Finally, school allows children with ASD and ID to improve their social and communicative skills in a natural setting, and thus, it can be more easily generalized to other situations of daily life [35].

Considering the French health care context, the study has two implications. First, we found significant improvements over time for most clinical variables in both groups. This means that the integrative care provided in day-care hospitals and medico-educational institutes allows most children with ASD and moderate to severe ID to improve their verbal communication, non-verbal communication, and social skills. This is in line with the largest observational three-year follow-up study using the CARS and VABS [36]. We showed that children with ASD significantly improved their developmental and interactional skills over time. Second, in the context of ongoing pressure from parents and advocacy organizations for more school inclusion for children with ASD [37], this study suggests that the DS1-EI
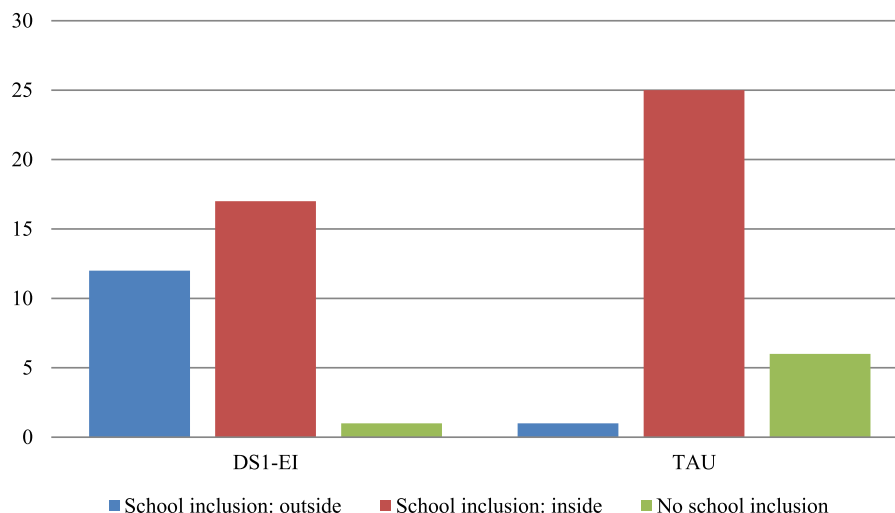

Fig. 2. School inclusion at 36 months (ITT analyses).

VABS-communication
p = 0.085

VABS-autonomy
p = 0.213

VABS-social
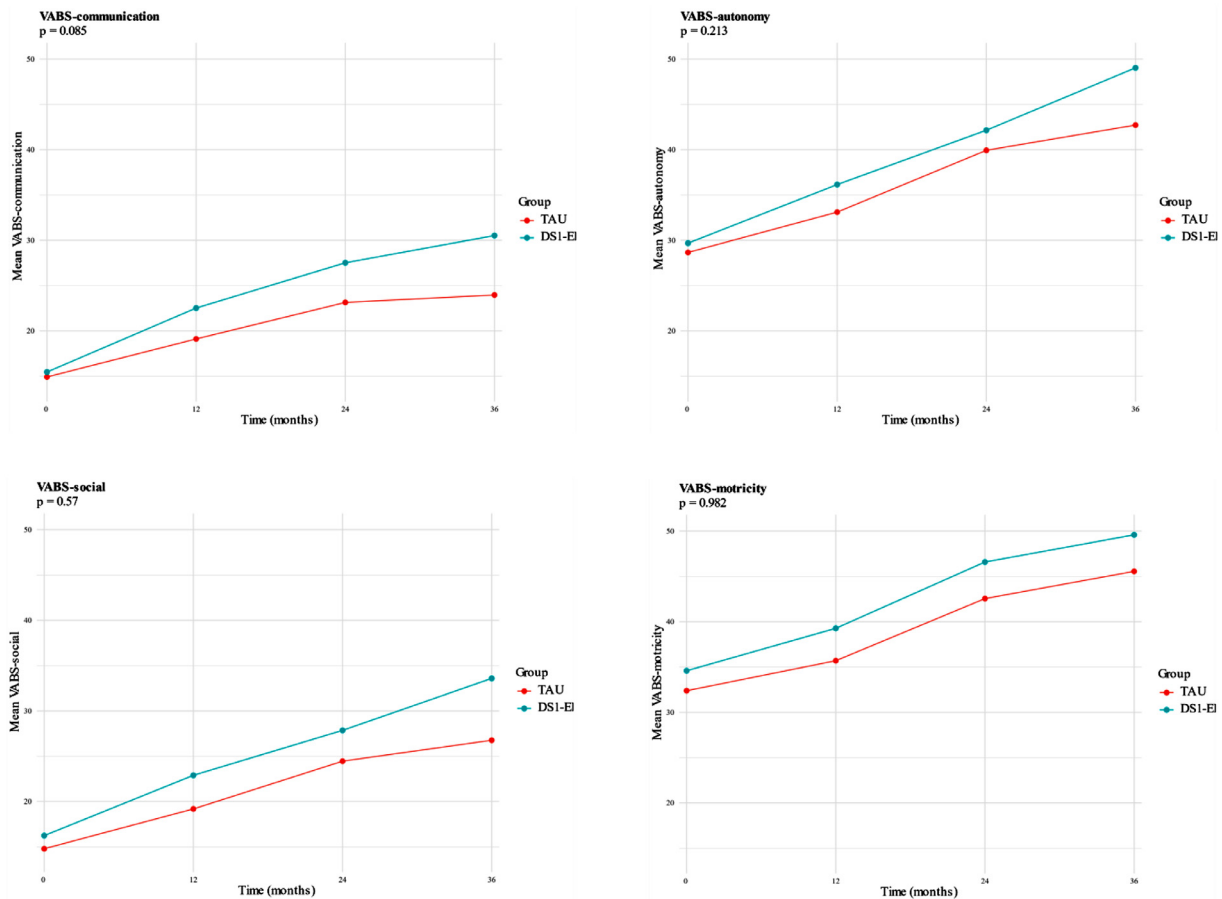p = 0.57

VABS-motricity
p = 0.982

Fig. 3. VABS evolution over time (PP analyses).

protocol is an effective intervention that could be used to support these populations throughout France.

Lack of generalization is a frequent issue in efficacy studies in ASD [38]. We hypothesize that the lack of significance in the group*time interaction may be due to (1) small effect sizes and insufficient sampling; (2) the high variance in subjects and evolution over time, which is a constant observation in ASD [39,40]; (3) the excessively short duration of the protocol; and (4) possible contamination between DS1-EI and TAU over a long treatment. As discussed by Yazdani and coll. in their review on early behavioural interventions, most studies using restrictive exclusion criteria (e.g. severe comorbidity) were more likely to report greater differences in terms of outcomes between experimental and control groups [41]. On one hand, using restrictive exclusion criteria increases the likelihood of showing the possible benefit of an intervention. On the other hand, it does not allow assessing whether the given intervention is adequate for all patients with ASD. Also, one may consider the 36-month trial duration to be substantial. However, we did not find significant differences between groups for VABS-communication in our preliminary analyses after 24 months [20], meaning that a trend for a significant course in favour of DS1-EI occurs between the second and the third year of exposure. The years of exposure needed for an intervention to show change have been seen in prior autism studies. For instance, in the PACT study, significant results of the parent-mediated communication-focused early intervention programme occurred five years after treatment initiation [9,10]. However, there is a debate on whether the changes can truly be seen as cascading effects due to the early PACT intervention.

Despite the strengths of the study (e.g., randomized design; multicentre recruitment; sample size; three-year duration; supervision and site monitoring for DS1-EI), it also had limitations. The main limitation is that patients' improvements could not be attributed to DS1-EI alone, as there were concurrent treatments and influences from the environment outside the health care institution. Second, we wanted to limit exclusion criteria given that many treatment studies restrict which participants can be included [3]. For example, we decided not to exclude children with comorbidities based on the idea that the DS1-EI intervention may be useful for all patients. However, including such a broad population of children with ASD and ID may have contributed to the large inter-patient variability observed. Indeed, our additional analyses regarding variables that predict changes in the two groups found that variables related to severity at the baseline (e.g., DQ, receiving a drug) had a negative impact on educational outcome. Finally, some secondary outcomes (e.g., VABS) could not be blindly rated, as explained in the methods section.

In conclusion, we conducted a 36-month prospective study to assess the benefit of the DS1-EI programme, a developmental and sequenced one-to-one educational intervention, in five- to nine-year-old children with ASD and moderate to severe ID. The setting was 11 day-care hospitals or medico-educational institutes throughout France. The study shows that DS1-EI implementation was feasible. Children who received the programme improved their academic skills and were more likely to be placed in mainstream classrooms than children receiving only TAU. However, generalization to clinical variables such as communication or social skills was not reached, but a tendency in PP analysis occurred for VABS-communication between the second and third years.

Author contributions

Study conception and design: CSG, AHB, GCC, DC; coordination and monitoring, data collection: AHB, AT, MNC, FS, CSG, ZG; statistical analysis and interpretation of the data: MP, HP, DC, CSG; drafting the

manuscript: CSG, MP, ZG, DC. All authors read and approved the final manuscript.

Declaration of Competing Interest

Acknowledgments

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Data sharing

Data directly supporting the study results will be available as excel files on the following publicly archived datasets (speapsl.aphp.fr) directly through this link: http://speapsl.aphp.fr/data_sharing/DS1-EI_data.xlsx

An annex will be available including all the variable names and definitions for easier use of the data set.

Supplementary materials

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.eclinm.2020.100537.

References

[1] American Psychiatric Association. Diagnostic and statistical manual of mental disorders (DSM-5®). Washington, DC: American Psychiatric Publishing; 2013.
[2] Reichow B, Barton EE, Boyd BA, Hume K. Early intensive behavioral intervention (EIBI) for young children with autism spectrum disorders (ASD). Cochrane Database Syst Rev 2012;10:eCD009260.
[3] Dawson G, Rogers S, Munson J, et al. Randomized, controlled trial of an intervention for toddlers with autism: the Early Start Denver Model. Pediatrics 2010;125: e17–23.
[4] Virues-Ortega J, Julio FM, Pastor-Barriuso R. The TEACCH program for children and adults with autism: a meta-analysis of intervention studies. Clin Psychol Rev 2013;33:940–53.
[5] Blanc R, Malvy J, Dansart P, Bataille M, Bonnet-Brilhault F, Barthélémy C. La thérapie d'échange et de développement, une rééducation neurofonctionnelle de la communication sociale. Neuropsychiatr Enfance Adolesc 2013;61:288–94.
[6] Goods KS, Ishijima E, Chang YC, Kasari C. Preschool based JASPER intervention in minimally verbal children with autism: pilot RCT. J Autism Dev Disord 2013;43:1050–6.
[7] Green J, Charman T, McConachie H, et al. Parent-mediated communication-focused treatment in children with autism (PACT): a randomised controlled trial. Lancet 2010;375:2152–60.
[8] Pickles A, Le Couteur A, Leadbitter K, et al. Parent-mediated social communication therapy for young children with autism (PACT): long-term follow-up of a randomised controlled trial. Lancet 2016;388:2501–9.
[9] Narzisi A, Costanza M, Umberto B, Filippo M. Non-pharmacological treatments in autism spectrum disorders: an overview on early interventions for pre-schoolers. Curr Clin Pharmacol 2014;9:17–26.
[10] Warren Z, McPheeters ML, Sathe N, Foss-Feig JH, Glasser A, Veenstra-Vanderweele J. A systematic review of early intensive intervention for autism spectrum disorders. Pediatrics 2011;127:e1303.
[11] Sandbank M, Bottema-Beutel K, Crowley S, et al. Project AIM: autism intervention meta-analysis for studies of young children. Psychol Bull 2020;146:1–29.
[12] Chamak B, Bonniau B, Oudaya L, Ehrenberg A. The autism diagnostic experiences of French parents. Autism 2011;15:83–97.
[13] Christensen DL, Baio J, Van Naarden Braun K, et al. Prevalence and characteristics of autism spectrum disorder among children aged 8 years–autism and developmental disabilities monitoring network, 11 sites, United States, 2012. MMWR Surveill Summ 2016;65:1–23.
[14] Salomone E, Beranová Š, Bonnet-Brilhault F, et al. Use of early intervention for young children with autism spectrum disorder across Europe. Autism 2016;20:233–49.
[15] Rattaz C, Munir K, Michelon C, Picot MC, Baghdadli A. School inclusion in children and adolescents with autism spectrum disorders in France: report from the ELENA French Cohort Study. J Autism Dev Disord 2020;50:455–66.
[16] Anderson CM, Smith T, Wilczynski SM. Advances in school-based interventions for students with autism spectrum disorder: introduction to the special issue. Behav Modif 2018;42:3–8.
[17] Lopata C, Thomeer ML, Rodgers JD, et al. Cluster randomized trial of a school intervention for children with autism spectrum disorder. J Clin Child Adolesc Psychol 2019;48:922–33.
[18] Panerai S, Zingale M, Trubia G, et al. Special education versus inclusive education: the role of the TEACCH program. J Autism Dev Disord 2009;39:874–82.
[19] Tanet A, Hubert-Barthelemy A, Crespin GC, Bodeau N, Cohen D, Saint-Georges C. A developmental and sequenced one-to-one educational intervention for autism spectrum disorder: a randomized single-blind controlled trial. Front Pediatr 2016;4:99.
[20] Tanet A, Hubert-Barthelemy A, Clément MN, et al. Developmental and sequenced one-to-one educational intervention (DS1-EI) for autism spectrum disorder and intellectual disability: a two-year interim report of a randomized single-blind multicenter controlled trial. BMC Pediatr 2020;20:263.
[21] Le Couteur A, Lord C, Rutter M. Autism diagnostic interview-revised. Los Angeles, CA: Western Psychological Services; 2003.
[22] Sparrow SS, Cicchetti DV, Balla DA, Doll EA. Vineland adaptive behavior scales: survey forms manual. Circle Pines, MN: American Guidance Service; 2005.
[23] Kaufman AS, Kaufman NL. Kaufman assessment battery for children. Circle Pines, MN: American Guidance Service; 2004.
[24] Ministère de l'éducation nationale, de la jeunesse et de la vie associative. Guide pour la scolarisation des enfants et adolescents handicapés, 2018. https://www.education.gouv.fr/sites/default/files/2019-11/guide-pour-la-scolarisation-des-enfants-et-adolescents-en-situation-de-handicap-1109.pdf(accessed June 8, 2020).
[25] Vygotsky LS. Mind in society: the development of higher psychological processes. Cambridge, MA: Harvard University Press; 1978.
[26] Schopler E, Reichler RJ, DeVellis RF, Daly K. Toward objective classification of childhood autism: childhood Autism Rating Scale (CARS). J Autism Dev Disord 1980;10:91–103.
[27] Schopler E, Lansing MD, Reichler RJ, Marcus LM. PEP-3 psychoeducational profile. Austin, TX: Pro-Ed. Inc.; 2005.
[28] Shaffer D, Gould MS, Brasic J, et al. A children's global assessment scale (CGAS). Arch Gen Psychiatry 1983;40:1228–31.
[29] R Core Team. R: a language and environment for statistical computing. Vienna, Austria: R Foundation for Statistical Computing; 2013.
[30] Chatham CH, Taylor KI, Charman T, et al. Adaptive behavior in autism: minimal clinically important differences on the Vineland-II. Autism Res 2018;11:270–83.
[31] Bitterman A, Daley TC, Misra S, Carlson E, Markowitz J. A national sample of preschoolers with autism spectrum disorders: special education services and parent satisfaction. J Autism Dev Disord 2008;38:1509–17.
[32] Midouhas E, Yogaratnam A, Flouri E, Charman T. Psychopathology trajectories of children with autism spectrum disorder: the role of family poverty and parenting. J Am Acad Child Adolesc Psychiatry 2013;52:1057–1065.e1.
[33] Interagency Autism Coordinating Committee (IACC). 2016-2017 Interagency autism coordinating committee strategic plan for autism spectrum disorder. https://iacc.hhs.gov/publications/strategic-plan/2017/(accessed June 8, 2020)
[34] Barton EE, Lawrence K, Deurloo F. Individualizing interventions for young children with autism in preschool. J Autism Dev Disord 2012;42:1205–17.
[35] Goldstein H. Communication intervention for children with autism: a review of treatment efficacy. J Autism Dev Disord 2002;32:373–96.
[36] Baghdadli A, Assouline B, Sonié S, et al. Developmental trajectories of adaptive behaviors from early childhood to adolescence in a cohort of 152 children with autism spectrum disorders. J Autism Dev Disord 2012;42:1314–25.
[37] Chamak B, Bonniau B. Trajectories, long-term outcomes and family experiences of 76 adults with autism spectrum disorder. J Autism Dev Disord 2016;46:1084–95.
[38] Lane JD, Lieberman-Betz R, Gast DL. An analysis of naturalistic interventions for increasing spontaneous expressive language in children with autism spectrum disorder. J Spec Educ 2015;50:49–61.
[39] Ben-Itzchak E, Zachor DA. Toddlers to teenagers: long-term follow-up study of outcomes in autism spectrum disorder. Autism 2020;24:41–50.
[40] Baghdadli A, Rattaz C, Michelon C, Pernon E, Munir K. Fifteen-year prospective follow-up study of adult outcomes of autism spectrum disorders among children attending centers in five regional departments in France: the EpiTED cohort. J Autism Dev Disord 2019;49:2243–56.
[41] Yazdani S, Capuano A, Ghaziuddin M, Colombi C. Exclusion criteria used in early behavioral intervention studies for young children with autism spectrum disorder. Brain Sci 2020;10(2):e99.