Research Review: Early intervention for infants and young children with, or at-risk of, autism spectrum disorder: a systematic review

Lorna French1 and Ellis M. M. Kennedy1,2
1Children, Young Adults and Families Department, Tavistock Clinic, London, UK; 2Research Department of Clinical, Educational and Health Psychology, University College London, London, UK

Background: There has been increased interest in early screening and intervention for young children with, or at risk of, autism spectrum disorder (ASD). This has generated a debate about the potential harms versus benefits of early identification and treatment. This review aims to identify the evidence base for early intervention in ASD. Methods: A systematic review searching for randomised controlled trials (RCTs) of interventions for children up to 6 years of age with, or at risk of, ASD was undertaken. Characteristics and outcomes of included studies were collated and described in tabular format, and all included studies were rated according to the Cochrane Risk of Bias Tool. Results: Forty-eight RCTs were identified, of which 40 were published since 2010. Most studies (n = 34) were undertaken in the United States. Included RCTs evaluated 32 different models of intervention. If blinding of participants and relevant personnel is overlooked as a source of bias, only six studies met criteria for low risk of bias across all domains of the Cochrane Risk of Bias Tool. The majority of studies had a relatively small sample size with only seven studies having a sample size >100. Conclusions: There has been a substantial increase in the number of RCTs evaluating early interventions in ASD. However, few studies, only 12.5% of the total, were rated as being at low risk of bias. Small sample size, unclear concealment of allocation and lack of clarity in the identification of the active ingredients in a diverse range of differently named treatment models were identified as challenges to the design, conduct and interpretation of studies. Improved co-ordination and design of studies is, therefore, required if future research in the field is to more clearly investigate the effects of early intervention for ASD. Keywords: Autism spectrum disorders; early intervention; randomised controlled trial design.

Introduction

In recent years, there has been an increased research interest in the early detection of signs of autism spectrum disorder (ASD) in infants and young children (Brian et al., 2008; Elison et al., 2014; Estes et al., 2015; Filliter et al., 2015; Gammer et al., 2015; Jones & Klin, 2013; Ozonoff et al., 2008; Sullivan et al., 2007; Wolff et al., 2014). Early detection of ASD may provide an important opportunity for timely intervention, which has been considered ‘essential to achieving the best outcomes’ (Pierce, Courchesne, & Bacon, 2016). While the American Academy of Pediatrics recommends universal screening for all children (Committee on Practice and Ambulatory Medicine, 2016), the US Preventative Services Taskforce (USPSTF) has now published recommendations stating that ‘current evidence is insufficient to assess the balance of benefits and harms of screening for ASD in young children for whom no concerns of ASD have been raised by their parents or a clinician’ (Siu & USPSTF 2016). This recommendation has prompted a robust debate about the benefits of screening and early treatment for young children with ASD (Pierce et al., 2016).

Proponents of early screening and intervention argue that early treatment may have the best chance of altering neural connectivity at a time of optimal brain plasticity (Pierce et al., 2016). Those advocating a more cautious approach refer to a lack of research evidence for the efficacy of treatment and question whether screening is associated with clinically important improvements in health outcomes (Siu & USPSTF 2016; UK National Screening Committee, 2016).

This debate around the pros and cons of early screening, identification and intervention is likely to be fuelled further by recent follow-up data indicating sustained improvements after early intervention. For example, 2-year follow-up after very early preemptive intervention for infants at familial high risk has shown reduced severity of autism prodromal symptoms at 3 years of age (Green et al., 2017). For young children with a prior diagnosis of ASD, 2-year follow-up postintervention with the Early Start Denver Model (ESDM) found improved core autism symptoms and adaptive behaviour at 6 years of age (Estes et al., 2015) and the more recent Preschool Autism Communication Trial (PACT) study is the first randomised controlled trial (RCT) to clearly demonstrate symptom reduction at long-term follow-up to middle childhood (7–11 years; Pickles et al., 2016). Such demonstration of sustained changes in autism symptoms is something that has previously been considered hard to achieve and may alter the balance of the current debate in favour of early screening, diagnosis and intervention.

Conflicts of interest statement: No conflicts declared.
This review has, therefore, been undertaken in the context of heightened interest in the potential for early intervention to improve outcomes for children with or considered at high risk of ASD (i.e. siblings of a child with ASD where recurrence risk is estimated to be between 10% and 20%; Szatmari et al., 2016). This has resulted in treatments for infants and young children being subjected to greater investigation in recent years representing a significant change compared to previous decades. A review in this journal 6 years ago on intervening in autism in infancy did not look at ASD-specific intervention studies, assuming a scarcity of empirically validated studies, but instead focused on treatment studies for infants with other developmental disorders or developmental risks (Wallace & Rogers, 2010).

Existing reviews of early treatment for ASD have focused exclusively on specific treatment models such as Applied Behavioural Analysis (Virués-Ortega, 2010) or the Early Start Denver Model (Ryberg, 2015; Waddington, van der Meer, & Sigafoos, 2016), on treatment approaches more broadly, e.g. behavioural interventions (Reichow, Barton, Boyd, & Hume, 2012; Warren et al., 2011), or on a particular mode of delivery such as parent-mediated interventions (Nevill, Lecavalier, & Stratis, 2016; Oono, Honey, & McConachie, 2013). These reviews have varied in the age range included, from under 3 to 4 years to up to 12 years of age with most focusing on children younger than 6 years. Two reviews that have looked at the full range of available treatment approaches have identified interventions for young children up to 2 and 3 years, respectively (Bradshaw, Steiner, Genqoux, & Koegel, 2015; Zwaigenbaum et al., 2015), and have included non-randomised studies. As far as we are aware this is the first systematic review to identify RCTs of interventions for young children up to 6 years of age and to include the full range of behavioural, developmental and combined, multicomponent treatment approaches. The purpose of this review therefore is to comprehensively identify the current evidence base for early treatment in ASD, scrutinising the strengths and limitations of that evidence and highlighting potential gaps that could be addressed in future research.

Methods

This review was guided by the Preferred Reporting Items for Systematic Reviews and Meta-Analyses standards for systematic review (PRISMA; Moher, Liberati, Tetzlaff, & Altman, 2009). A literature search was conducted using the electronic databases PubMed and PsyINFO (1806 to present) up to and including May 10, 2017. We chose to use wide search terms to capture a range of literature that could then be evaluated more extensively. The search terms used were: ‘autism[TAIB] OR ASD[TAIB] OR ASC[TAIB]’ OR ‘autistic [TAIB]’ AND ‘intervention[TAIB]’ OR ‘treatment[TAIB]’ AND ‘(child* OR infant* OR toddler* OR pre*school* OR nurser*) AND (RCT* OR randomiz* OR randomis*)’. In addition, comprehensive manual searches of reference lists of included studies, reviews and researcher websites were undertaken.

As middle childhood is generally defined as age 6 years and above, and the aim was to identify interventions for infants and young children, we chose to include all randomised controlled trials that focused on participants up to the age of 6 years (≤72 months) that had a diagnosis, or were at high risk of a diagnosis, of ASD. We included high risk children due to the increasing interest in the early emergence of ASD symptoms and atypical developmental trajectories in specific domains (e.g. slower growth in initiating joint attention) in a proportion of infant siblings of children with autism (Szatmari et al., 2016). We included studies in which all participating children met both age and diagnostic/risk criteria. RCTs were required to have evaluated an early intervention programme or treatment for young children with autism, included one or more comparators of wait-list controls, treatment as usual controls or additional treatment groups, and included child outcome measures that assess symptoms of ASD. While we did not restrict the search by style of approach, we excluded studies focused on pharmacological, dietary or medical treatments. With regard to multiple publications of the same initial RCT, only the initial publication was included in this review. The search was not limited by language or publication date.

Data were extracted using a coding form detailing characteristics of comparisons, interventions, dose and approach of intervention, intervention type and associated outcomes. Principal outcomes of interest focused on the effects on core symptoms of ASD, whether focused on one area or multiple levels of functioning. These descriptive data were collected in tables that are available as supporting information (Table S1).

Risk of bias across included studies was assessed using the Cochrane Risk of Bias Tool (Higgins & Green, 2011). This tool allowed us to create a visual representation of domains within the validity assessment that could cause risk of bias when considering the outcomes of each study. All studies were double-rated and disagreements were resolved through discussion. Results were recorded in a ‘Risk of Bias’ table with a brief rationale for each decision. The table has been provided as supporting information (Table S2). Each study was assessed and assigned ‘low risk’, ‘unclear risk’ or ‘high risk’ in each of the following domains of bias: selection bias (lack of random sequence generation and allocation concealment), performance bias (lack of blinding of participants and relevant personnel), detection bias (lack of blinding of outcome assessment), attrition bias (lack of complete outcome data and/or inappropriate analysis to account for attrition), reporting bias (incomplete reporting of specified outcomes) and ‘other sources of bias’. For detection bias, we have judged that if the primary outcome relies on participant report, and have therefore rated the study at ‘high risk’ of detection bias. However, if the assessor of the primary outcome is blind to treatment allocation then we have judged that this is likely to be sufficient to protect against bias, even if a secondary outcome relies on participant report, and have therefore rated the study overall at a ‘low risk’ of detection bias. For the ‘other sources of bias’ domain, we chose to rate the following characteristics as causing ‘high risk of bias’: (a) studies with treatment groups with <15 participants, (b) studies using cluster randomisation that did not account for clustering in the analysis, and (c) studies that did not prespecify primary and secondary outcomes.

Due to the considerable heterogeneity of interventions and outcome assessments, a meta-analysis was not conducted. Results are presented by age range of included participants: infants (0–18 months), toddlers (18–36 months) and young children (37–72 months). Tables describing characteristics of all included studies are available as supporting information (Tables S1 and S4). Descriptions and outcomes of studies that met criteria for ‘low risk of bias’ across all domains other than
performance bias are reported here. Performance bias has been overlooked for the purpose of reporting these studies as it is commonly not possible to blind parents, teachers or trainers, and therefore, all included studies present with comparatively equal risk of bias in this area.

Results
Our initial search yielded 1,339 articles (Figure 1). After duplicates were removed, 858 articles were excluded through evaluation of the title and abstract. One hundred sixty-six remaining articles were then retrieved in full, where 118 failed to meet inclusion criteria (for those studies that met multiple exclusion criteria, the first identified area for exclusion is noted as reason for exclusion). Of these 118 articles, 64 were excluded on the basis of age range, 40 for study design (including additional analyses of previously published RCTs), six on the basis of intervention type, six for focusing on outcomes not related to core features of ASD, one for an ineligible population group, and one on the basis of inability of the authors to retrieve the article in full (Zhang et al., 2009). The remaining 48 studies evaluated 32 different intervention models delivered to children up to the age of 6 with, or at-risk of, a diagnosis of autism.

Settings and participants
Randomised controlled trials evaluated interventions in the home ($n = 13$); in educational or child-
Intervention delivery

Interventions were delivered by trained therapists, teaching staff, or research staff, with the majority involving both parent training and direct work with the child. Hours of intervention varied widely, with the minimum being a total of 6 hr (JASPER; Lawton & Kasari, 2012), and the maximum being 40 hr per week for 4 years (UCLA Lovaas Method; Sallows & Graupner, 2005). Only seven RCTs focused on parent training with no contact with children, although these often involved a requirement for parents to practise daily with their children, and the majority (n = 27) used a combination of child- and parent-directed intervention. Fourteen RCTs involved intervention approaches that did not include contact with parents.

Interventions

The most tested intervention model by far was the Joint Attention Symbolic Play Engagement and Regulation (JASPER; Kasari, Freeman, & Paparella, 2006), with 11 RCTs including two during which the model itself was refined and developed (Kaaale, Smith, & Sponheim, 2012; Kasari et al., 2006). Of the 32 models tested in the RCTs (Table S4), there were 6 with a predominantly behaviourally approach, 11 with a developmental approach, 12 with a combined multicomponent approach (e.g. with both developmental and behavioural elements), two with a strongly technology-based approach, and one augmentative and alternative communication technique.

Description of studies by age of participants

Characteristics and outcomes of all included studies are reported in tables that are available as supporting information (Table S1). Descriptions of studies that met criteria for ‘low risk of bias’ across all domains of bias excepting performance bias are reported here in full.
communication (Dawson et al., 2010; Rogers et al., 2012). Another three RCTs (Kasari et al., 2010, 2015; Shire et al., 2017) assessed the JASPER intervention, which aims to sustain periods of joint attention and increase joint attention gestures and play skills. The remaining eight studies looked at a range of different models: (a) Autism 1-2-3, a parent and child behavioural approach (Wong & Kwan, 2010); (b) Joint Attention Mediated Learning, an intervention addressing the social functions of pre-verbal communication (Schertz et al., 2013); (c) Group and individual Early Social Interaction interventions based on the Social Communication, Emotional Regulation, and Transactional Supports (SCERTS) curriculum (Wetherby et al., 2014); and (d) Multicomponent parent-training programmes such as Focused Playtime Intervention (FPI; Kasari, Siller et al., 2014), Hanen’s More Than Words (Carter et al., 2011), Interpersonal Synchrony (Landa et al., 2011), the Social-Pragmatic Joint Attention Focused Parent Training Programme (Drew et al., 2002), and Treatment and Education of Autistic and related Communication handicapped Children (TEACCH; Welterin et al., 2012).

One study met criteria for 'low risk of bias' across all domains of bias excepting performance bias (Shire et al. 2017). Shire et al. (2017) randomly assigned 113 children, aged 24–36 months, with a diagnosis of ASD/PDD-NOS to either a JASPER treatment group or a wait-list control group in an early intervention setting. The JASPER treatment group received 30 min every day of individual support from teaching assistants (TAs) which focused on engaging the child by creating play routines through imitation and modelling of new play acts. The wait-list control group received a treatment-as-usual control condition. Two studies used a developmental, parent-mediated communication programme, first in a pilot study (Aldred et al., 2004) and later in the PACT (Green et al., 2010); two studies investigated a Developmental, Individual-Difference, Relationship-Based (DIR) intervention which focuses on relationships, social skills, meaningful, spontaneous use of language and communication, and integrated understanding of human development (Casenbiser et al., 2013; Pajareya & Nopmaneejumruslers, 2011); two used the UCLA Lovaas Model of ABA, which uses learning theory to change social behaviour (Sallows & Graupner, 2005; Smith et al., 2000); three studies used Pivotal Response Training which targets the development and spontaneous use of functional spoken language (pivotal response treatment, PRT; Nefdt et al., 2010; Schreibman & Stahmer, 2014; Hardan et al., 2015); and two used the Picture Exchange Communication System which teaches children to use pictures to communicate (PECS; Yoder & Stone, 2006; Schreibman & Stahmer, 2014).

Eight studies used variations of the JASPER intervention (Chang et al., 2016; Goods et al., 2013; Gould, 2015; Kaale et al., 2012; Kasari et al., 2006; Kasari, Lawton et al., 2014; Lawton & Kasari, 2012; Roberts et al., 2011; Rogers et al., 2006; Strain & Bovey II, 2011; Tonge, Breton, Kiomall, Mackinnon, & Rinehart, 2014; Wong, 2013; Young, Falco, & Hanita, 2016), seven used behavioural approaches (Gould, 2015; Hardan et al., 2015; Ingersoll, 2010; Nefdt, Koegel, Singer, & Gerber, 2010; Sallows & Graupner, 2005; Schreibman & Stahmer, 2014; Smith, Groen, & Wynn, 2000), 10 used developmental approaches (Aldred, Jonathan, & Catherine, 2004; Carter et al., 2011; Green et al., 2010; Lim, 2010; Pajareya & Nopmaneejumruslers, 2011; Poslawsky et al., 2015; Rogers et al., 2006; Solomon, Van Egeren, Mahoney, Quon Huber, & Zimmerman, 2014; Thompson, McFerran, & Gold, 2014; Yoder & Stone, 2006), two used technology-based approaches (Fletcher-Watson et al., 2016; Whalen et al., 2010), and two used an augmentative and alternative communication approach (Schreibman & Stahmer, 2014; Yoder & Stone, 2006).

The remaining studies again used a range of models and approaches: (a) The Autism Preschool Program, which taught parents how to perform a functional analysis of behaviour and to plan and evaluate strategies for changing behaviour (Jocelyn et al., 1998); (b) Comprehensive Autism Program, a combination of a number of interventions used throughout the day at school, short, one-to-one

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sessions with teachers, and parent education workshops (Young et al., 2016); (c) Developmental Speech-Language Training Through Music, a programme designed to enhance speech and language development (Lim, 2010); (d) PROMPT, a neurodevelopmental approach for speech production disorders (Rogers et al., 2006); (e) ESDM (Rogers et al., 2006); (f) Family Centred Music Therapy (FCMT), which encourages parents to interact with their child in music-making activities (Thompson et al., 2014); (g) FindMe, an app developed to aid social communication skills (Fletcher-Watson et al., 2016); (h) Discrete Trial Training, a structured behavioural teaching method that uses clearly defined, scripted steps (Gould, 2015); (i) Home and centre-based Building Blocks intervention, aimed to improve social communication by a variety of approaches (Roberts et al., 2011); (j) Learning Experiences and Alternative Program for Preschoolers and their Parents (LEAP) which is utilised within schools and includes skills training for families (Strain & Bovey, 2011); (k) Parent education and behaviour management (PEBM), which promotes parental coping skills, discussion, understanding of developmental levels, and making use of positive behaviour support principles (Tonge et al., 2014); (l) and Parent education and counselling (PEAC), in which parents were given educational material and emphasis was placed on counselling (Tonge et al., 2014); (m) Play and Language for Autistic Youngsters (PLAY) model, a parent-mediated developmental model focused on social reciprocity (Solomon et al., 2014); Reciprocal Imitation Training (RIT), an intervention developed to teach children to imitate during play (Ingersoll, 2010); (n) Responsive Education and Prelinguistic Milieu Teaching (RPMT), a programme designed to facilitate intentional communication (Yoder & Stone, 2006); (o) TEACCH-based group social skills training (Ichikawa et al., 2013); (p) TeachTown: Basics, a programme including computer lessons and natural environment activities (Whalen et al., 2010); (q) VIPP-AUTI, a video feedback intervention aiming to enhance parental sensitivity to their child’s signals (Poslawsky et al., 2015).

Four of the 32 studies met criteria for ‘low risk of bias’ across all domains of bias with the exception of performance bias: Green et al. (2010), Poslawsky et al. (2015), Fletcher-Watson et al. (2016) and Hardan et al. (2015).

Green et al. (2010) randomly assigned 152 children meeting criteria for core autism, aged 24–59 months, to a parent-mediated communication-focused treatment (PACT) or treatment as usual. The PACT intervention aimed to increase parental sensitivity and responsiveness to child communication, reduce mistimed responses using video feedback, and promote a range of helpful strategies (e.g. familiar repetitive language). Families attended biweekly 2-hour clinic sessions for 6 months followed by monthly booster sessions for 6 months. There was a between group effect size of −0.24 (95% CI −0.59 to 0.11) for the primary outcome measure (ADOS-Generic social communication algorithm score). Severity of symptoms was reduced by 3.9 points (SD 4.7) on the ADOS-Generic algorithm in the PACT group, and 2.9 (3.9) in the group assigned to treatment as usual. Treatment effect was positive for parental synchronous response to child, child initiations with parent, and for parent–child shared attention.

Poslawsky et al. (2015) randomly assigned 78 children with ASD, aged 16–61 months, to either the Video feedback Intervention to Promote Positive Parenting adapted to Autism (VIPP-AUTI) intervention or home-based nursing care. VIPP-AUTI utilises video feedback to encourage parents to reflect on interactions with their children with an emphasis on positive, successful interactions, and aims to enhance parent sensitivity to their child’s signals. The intervention included five home visits of 60–90 min every 2 weeks and occurred over a 3-month period. Parent–child interaction, as measured on the parental Emotional Availability Scale (EAS), was assessed as the primary outcome. Parents who received the VIPP-AUTI programme showed decreased intrusiveness on the EAS, whereas intrusiveness increased in the control group (F(1, 72) = 4.30, p = .04, η² = .06, d = .49). Parental sensitivity and parental structuring (also measured by the EAS) did not show significant intervention effects. At 3-month follow-up, intervention effects were found on child initiated joint attention skills (as measured by the Early Social and Communication Scales), but no significant group differences were found on other aspects of parent–child interaction or child play behaviour.

Fletcher-Watson et al. (2016) randomly assigned 54 children with ASD, aged up to 6 years, to either an intervention group using the ‘FindMe’ iPad™ application or a wait-list control group. The FindMe application was designed to give children an opportunity to rehearse attending to people and following social cues. Parents of children assigned to the intervention group were instructed to aim for approximately 5 minutes of game play per day for 2 months. The primary outcome measure was the Brief Observation of Social Communication Change (BOSCC), a comprehensive coding system that provides an overall score and a social communication score to measure change in autistic behaviours. No significant differences were found between intervention and control groups for the overall BOSCC score [difference in means = −2.04 (−5.84 to 1.77), p = .288] or the BOSCC social communication score [difference in means = −0.78 (−3.44 to 1.89), p = .561], or for any secondary measures of autistic behaviours and communication.

Hardan et al. (2015) randomly assigned 53 children with ASD, aged 2–6 years, to a PRT or a psychoeducation control group. PRT was delivered in weekly 60- to 90-min sessions for 12 weeks and
taught parents to target functional communication deficits. The primary outcome measures were child frequency of utterances (and whether these were prompted) and parent fidelity of treatment implementation, as measured during a structured laboratory observation. Children in the PRT group demonstrated greater improvement in frequency of utterances ($F(2, 43) = 3.53, p = .038, d = .42$), and 84% of parents in the PRT group met fidelity criteria. Children in the PRT group also demonstrated greater improvement on secondary measures of the Vineland Adaptive Behaviour Scales (VABS) communication score and the Clinical Global Impression Scale (CGI-S) severity and improvement scores. Significant differences were not demonstrated between groups for further secondary outcomes: the MacArthur-Bates Communicative Development Inventories (MCDI), the Social Responsiveness Scale (SRS), and the Preschool Language Scale, 4th Edition (PLS-4).

Discussion

As far as we are aware, this is the first systematic review to comprehensively look at the evidence base for early intervention in ASD, encompassing the full range of available treatment modalities and including infants and young children up to 6 years of age. What is most striking is the sheer volume of RCTs published since 2010 (Figure 2). Forty of a total of 48 RCTs have been published since 2010 (Figure 2), and 34 studies have been undertaken in the United States (Figure S2), most probably reflecting the increased interest in early screening and intervention in the States (Pierce et al., 2016).

While the majority of studies (32 studies) included children in the 3- to 6-year age range, 13 studies focused solely on children under 3 years, and only three focused on infants up to 18 months. Two of three of the studies evaluating intervention in infancy were published in 2015 (Baranek et al., 2015; Green et al., 2015) indicating an emerging emphasis on very early intervention in recent years.

Of the 48 studies identified, only six studies met criteria for low risk of bias across all achievable domains of the Cochrane Risk of Bias Tool, representing only 12.5% of the total (Higgins & Green, 2011; Risk of Bias Tool; Green et al., 2010; Poslasky et al., 2015; Fletcher-Watson et al., 2016; Green et al., 2015; Hardan et al., 2015; Shire et al., 2017; Figure 3). Lack of blinding of outcome assessment and failure to specify a method of allocation concealment were common methodological concerns across the remaining RCTs.

A further challenge to the field is the diversity of treatment approaches with a confusing variety of names. Thirty-two different models were identified (Table S4), many drawn from a range of approaches and containing multiple components, complicating the process of comparing models and identifying successful ingredients of an intervention. Some interesting efforts to isolate and test potential ‘active ingredients’ of interventions are now being made (Gulsrud, Hellemann, Shire, & Kasari, 2016); however, the sheer volume of separately developed and named interventions, and the lack of co-ordination around this, is likely to hinder the identification of programmes appropriate for further evaluation and implementation in routine practice.

Heterogeneity of participating children and a wide variation across outcome measures as well as interventions was a challenge to comparison, as in previous reviews (Warren et al., 2011; Zwaigenbaum et al., 2015). There was also great disparity in the ‘dose’ of intervention, ranging from a total of 6 hours of intervention (Lawton & Kasari, 2012) to 40 hours per week for 4 years (Sallows & Graupner, 2005). Despite this significant heterogeneity, other reviewers have successfully conducted meta-analyses, for example, with parent-mediated interventions with similar outcome measures (Nevill et al., 2016; Oono et al., 2013) or controlled clinical trials assessing early intensive behavioural interventions (Reichow et al., 2012). Future reviews may use this strategy to analyse subgroupings of the research studies identified in this review, such as the evidence base for JASPER, and produce additional, meaningful comparisons of the RCT literature.

Although treatment effects were significant in many cases, effect sizes were usually small with wide confidence intervals, demonstrating the variability of outcomes and the need for additional, good-quality research. Heterogeneity across outcome measures also impacts on the ability to draw meaningful conclusions with regard to treatment effectiveness. There was substantial variation in utilised measures, with a total of 87 different outcome measures used across 48 studies (excluding fidelity and satisfaction measures; for further details, see supporting information). Many of these measures also include a
## Cochrane Risk of Bias Tool, Table of Results

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number of subscales, with some being prioritised within some trials and disregarded in others. Such lack of agreement on outcome measures, in conjunction with inconsistent methodological quality, makes meta-analysis a significant challenge.

Improving the quality of future research is, therefore, of great importance. Specifically, concerns with allocation concealment commonly arose as a factor increasing the risk of bias (Figure 3). As many research groups conducted studies investigating models and interventions developed by the researchers or department, increased risk for selection bias is of particular importance. Another key issue was sample size (Figures 3 and Figure S1), and therefore power to detect a treatment effect. Only seven RCTs included over 100 participants, one of which had three treatment arms and therefore low numbers in each comparison group (Tonge et al., 2014), and three of which were larger, cluster randomised trials (Shire et al., 2017; Strain & Bovey, 2011; Young et al., 2016). Cluster randomisation was also utilised in two smaller studies (Whalen et al., 2010; Wong, 2013). While this method of randomisation does not necessarily invalidate statistical procedures, analyses must be properly adjusted to account for higher similarity between participants within clusters. Only two studies clearly outlined their statistical procedure for accounting for cluster randomisation (Shire et al., 2017; Strain & Bovey, 2011), and the remaining trials may, therefore, be given inappropriate weight in any future meta-analyses.

With regard to potential implications for treatment, five of the six studies identified in this review as being at low risk of bias show promising findings (Green et al., 2010, 2015; Hardan et al., 2015; Poslawsky et al., 2015; Shire et al., 2017) and two
demonstrate treatment effects at long-term follow-up (Green et al., 2010, 2015). While these findings are encouraging, all of these approaches (particularly those demonstrating clear effects at long-term follow-up) warrant further research evaluation and investigation in routine clinical practice. In addition, meta-analyses of approaches that have been more substantially tested (e.g. JASPER; Table S4) will further clarify the evidence base.

Clearly for a neurodevelopmental condition such as ASD, follow-up over the long-term is of immense importance. To our knowledge, seven of the 48 included studies have as yet published longer-term follow-up findings with follow-up periods of 3 months (Gengoux et al., 2015), 1 year (Kaale, Fagerland, Martinsen, & Smith, 2014; Pajareya & Nopmaneejumruslers, 2012), 2 years (Estes et al., 2015; Green et al., 2017), 5 years (Kasari, Gulsrud, Freeman, Paparella, & Hellemann, 2012) and almost 6 years (Pickles et al., 2016). As sustained effects on targeted outcomes are uncommon for developmental interventions (Pickles et al., 2016), future early intervention research would benefit from the inclusion of long-term follow-up (Matson & Konst, 2013).

Consideration of outcome measures is also key in identifying successful interventions. In the case of the PACT study, a clearer demonstration of treatment effect at follow-up may be attributable to the use of ADOS severity scores as opposed to the ADOS-Generic used in the initial trial (Pickles et al., 2016; Sigafoss and Waddington, 2016). Identifying suitable outcome measures that capture meaningful change and minimise risk of bias is a substantial future challenge for clinicians and researchers alike, especially as those measures with the greatest external validity (e.g. caregiver report) are susceptible to performance bias (Fletcher-Watson & McConachie, 2017; see Figure 3).

The unprecedented interest in early intervention in ASD, as demonstrated by the 48 RCTs identified in this review, highlights the pressing need for further investigation to enable greater discrimination around what specific approach is most likely to be effective for any individual child and their family. Critical ingredients of successful interventions should be examined, particularly as these may vary between individuals within such a heterogeneous population (Gulsrud et al., 2016; Sigafoss and Waddington, 2016; Loth et al., 2017).

**Conclusion**

This review comprehensively identifies the current evidence base for early and very early intervention in ASD. The review highlights the large number of studies, over 83% of the total, published since 2010, reflecting the heightened interest in recent years in the potential for early intervention to alter developmental trajectories in this common neurodevelopmental condition. Few studies were rated as being at low risk of bias pointing to considerable challenges for the future research in the field to undertake well-designed and co-ordinated research to better investigate the effects of interventions for ASD in infancy and early childhood.

**Supporting information**

Additional Supporting Information may be found in the online version of this article:

- Figure S1. Bar graph depicting number of participants.
- Figure S2. Bar graph depicting RCTs by country of affiliation of lead author.
- Table S1. Characteristics and outcomes of included studies.
- Table S2. Risk of bias assessments.
- Table S3. Excluded studies.
- Table S4. Included interventions.

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**Correspondence**

Eilis M. M. Kennedy, Children, Young Adults and Families Department, Tavistock Clinic, 120 Belsize Lane, London NW3 5BA, UK; Email: ekennedy@tavi-port.nhs.uk

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**Key points**

- There is controversy around the potential benefits and harms of early screening and intervention in ASD.
- This review comprehensively identifies the research evidence for early intervention.
- Forty-eight RCTs were identified of which the overwhelming majority, 40, were published since 2010.
- Thirty-two different models of intervention were evaluated.
- 12.5% of RCTs met criteria for low risk of bias across all achievable domains of the Cochrane Risk of Bias Tool.
- Improved quality and co-ordination of research are major challenges to be overcome if future research is to better investigate the effects of early intervention for ASD.
Early intervention for autism

References


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