APPENDIX 14B: CLINICAL EVIDENCE –STUDY CHARACTERISTICS TABLES: INTERVENTIONS AIMED AT CORE FEATURES OF AUTISM

1.1 CHARACTERISTICS OF INCLUDED PSYCHOSOCIAL INTERVENTION STUDIES

1.1.1 ALDRED2001/2004

Study ID	ALDRED2001/2004
Bibliographic reference	Aldred C, Pollard C, Phillips R, Adams C. Multidisciplinary social communication intervention for children with autism and pervasive developmental disorder: the Child's Talk project. Educational and Child Psychology. 2001;18:76-87. Aldred C, Green J, Adams C. A new social communication intervention for children with autism: pilot randomised controlled treatment study suggesting effectiveness. Journal of Child Psychology and Psychiatry. 2004;45:1420-1430.
Methods	**Allocation:** Randomised **Matching:** Stratified randomisation based on chronological age and severity of baseline autistic behaviours (as measured by the Autism Diagnostic Observation Schedule [ADOS]) **Blindness:** Researchers and outcome assessors were blind to group assignment. However, participants, intervention administrators and parents were non-blind **Setting:** Not reported **Raters:** Parent-completed, parent-interview and blinded educational psychologist and educational audiologist **Country:** UK
Participants	**Diagnosis:** Autistic disorder **Coexisting conditions:** None reported **Qualifying Diagnostic Assessment:** Clinical diagnosis of autistic disorder and meeting full diagnostic criteria for classical autism on the Autism Diagnostic Interview (ADI) **N:** 28 **Age:** 2-5.9 years (means not reported. Median ages: 4 years for experimental group and 4.3 years for control group) **Sex:** 11% female **Ethnicity:** 93% white **IQ:** Not reported **Inclusion criteria:** Participants needed to: be aged 2-5.9 years; have a clinical diagnosis of autistic disorder; and meet full diagnostic criteria for classical autism on the ADI to be included in the study **Exclusion criteria:** Participants were excluded if they had: severe global developmental delay; severe environmental deprivation in infancy; diagnosed hearing impairment; or diagnosed visual impairment. Participants were also excluded if their parents had known chronic psychiatric or physical illness or if their first language was not English or if the participant showed no evidence of any desire to interact with an adult
Interventions	**Experimental Intervention: Child's Talk intervention (Aldred et al., 2001).** This intervention was developed by Aldred and colleagues and aimed to increase the quality of parental adaptation and communication with their autistic children. Techniques included initial psychoeducation (teaching parents about the developmental stages of early social communication)

	followed by parent-child sessions in which parents were encouraged to establish shared attention between themselves and their child, decrease intrusive demands they made on their child, model language output based on child capabilities and consolidate and expand their child's social communication by establishing predictable routines and repetition in rehearsed interactive play and adding variations and expansions to the child's play and language, i.e. leaving openings for child to fill with a social and verbal response. **Delivery of intervention:** The group size and the individual administering the intervention are not reported **Format or method of administration:** Not reported **Intensity:** Number of hours of intervention not reported (parents and children attended monthly intervention sessions for 6 months, followed by a further 6 months of less frequent maintenance sessions) **Duration of intervention:** 52 weeks **Total duration of follow-up:** 52 weeks
Outcomes	**Direct outcome:** **Core autism feature: Impaired reciprocal social communication and interaction** (as measured by the ADOS-Reciprocal social interaction sub-domain; and behavioural observations of child communication acts and child shared attention) **Indirect outcomes:** **Core autism feature: Overall autistic behaviours** (as measured by the Autism Diagnostic Observation Schedule [ADOS]-Total score) **Coexisting problems or disorders: Adaptive behaviour** (as measured by the Vineland Adaptive Behaviour Scales [VABS] - Communication subscale); **Speech and language** (as measured by the MacArthur Communication Development Inventory [CDI]: Words and Gestures - Language comprehension and Expressive language subscales)
Study Design	RCT
Source of funding	Shirley foundation
Limitations	1. Risk of selection bias is unclear/unknown as the randomisation method was unclear 2. High risk of performance bias as the individual administering the intervention is not blind to group assignment 3. High risk of response bias as participants are not blind to group assignment 4. Risk of detection bias is different for different outcome measues but is unclear/unknown for VABS as based on parent report rather than direct behavioural observation and high risk for CDI as parent-completed 5. High risk of selective reporting bias as data could not be extracted for the ADOS communication subdomain and ADOS stereotyped and restricted behaviours subdomain, or the Parenting Stress Index
Notes	Contacted author regarding missing outcome data and no reply. Data were not extracted for parent synchrony, parent asynchrony, parent communication acts or parent shared attention as given that the intervention was caregiver-mediated these outcome measures were fidelity measures rather than measures of clinical efficacy.

1.1.2 BASS2009

Study ID	BASS2009
Bibliographic reference	Bass MM, Duchowny CA, Llabre MM. The effect of therapeutic horseback riding on social functioning in children with autism. Journal of Autism and Developmental Disorders. 2009;39:1261-1267.
Methods	**Allocation:** Randomised **Matching:** No matching **Blindness:** Non-blind **Setting:** Good Hope Equestrian Training Centre (GHETC) **Raters:** Parent-rated **Country:** USA
Participants	**Diagnosis:** DSM-IV-TR ASD (6% Asperger's disorder, 32% mild ASD, 47% moderate ASD, 15% severe ASD) **Coexisting conditions:** None reported **Qualifying Diagnostic Assessment:** None reported **N:** 34 **Age:** 4-10 years (mean: 7.3 years) **Sex:** 15% female **Ethnicity:** Not reported **IQ:** Not reported **Inclusion criteria:** Not reported **Exclusion criteria:** Not reported
Interventions	**Experimental Intervention: Horseback riding intervention.** Participants were trained in: mounting and dismounting (aimed at stimulating verbal communication, proprioception and vestibular processing); warm-up exercises; riding skills (aimed at stimulating sensory seeking, balance and coordination, and fine and gross motor skills); individualized and group games while on the horse, such as "Simon says" and catch and throw (aimed at developing social and communication skills); and grooming activities. Throughout the intervention participants were verbally and physically reinforced (for instance, with high-fives and hugs). **Delivery of intervention:** Intervention delivered by trained GHETC instructors. Group size not reported **Format or method of administration:** Group-based **Intensity:** 12 hours (1 hour/week) **Duration of intervention:** 12 weeks **Total duration of follow-up:** 12 weeks
Outcomes	**Direct outcome:** **Core autism feature: Impaired reciprocal social communication and interaction** (as measured by Social Responsiveness Scale [SRS] - Total score, and Social Cognition, Social Awareness, and Social Motivation subscales) **Indirect outcomes:** **Behaviour that challenges** (as measured by the Sensory Profile - Inattention/distractability and Sedentary subscales) **Coexisting problems or disorders: Fine and gross motor skills** (as measured by the Sensory Profile - Fine motor/perception subscale); **Sensory sensitivities** (as measured by the Sensory Profile - Total score, and Sensory seeking, and Sensory sensitivity subscales)
Study Design	RCT

Source of funding	Not reported
Limitations	1. Risk of selection bias is unclear/unknown as randomisation method is unclear and insufficient detail reported with regards to allocation concealment 2. High risk of performance bias as intervention administrators non-blind 3. High risk of response bias as participants non-blind 4. High risk of detection bias as outcome measures parent-rated and parents non-blind 5. High risk of selective reporting bias as data not reported for selected subscales: the social communication and autistic mannerisms subscales of the Social Responsiveness Scale (SRS); and the emotionally reactive, low endurance/tone, oral sensory sensitivity, and poor registration subscales of the Sensory Profile scale
Notes	Not applicable

1.1.3 BEAUMONT2008

Study ID	BEAUMONT2008
Bibliographic reference	Beaumont R, Sofronoff K. A multi-component social skills intervention for children with Asperger syndrome: the Junior Detective Training Program. Journal of Child Psychology and Psychiatry. 2008;49:743-753.
Methods	**Allocation:** Randomised **Matching:** No matching **Blindness:** No blinding of participants, individuals responsible for administering care or outcome assessors reported **Setting:** Academic **Raters:** Clinicians and parents **Country:** Australia
Participants	**Diagnosis:** DSM-IV-TR Asperger Syndrome **Coexisting conditions:** None reported **Qualifying Diagnostic Assessment:** Confirmed diagnosis from a paediatrician, along with a battery of parent-rated questionnaires which included diagnostic items and the Childhood Asperger Syndrome Test (CAST). **N:** 49 **Age:** Range: 7.5-11.7 years. (Mean age: 9.7) **Sex:** 10% female **Ethnicity:** Not reported **IQ:** Range not reported (mean 107.3).WISC-III **Inclusion criteria:** Children were included if they: were aged 7.5-11 years; had a diagnosis of Asperger's Syndrome confirmed by a paediatrician and parent-completed Childhood Asperger Syndrome Test (CAST); had a WISC-III pro-rated IQ score >=85 **Exclusion criteria:** None reported
Interventions	**Experimental Intervention: Junior Detective Training Program.** Intervention consisted of a computer game which aimed to teach children emotion recognition, emotion regulation and social interaction skills using computer-animated and human characters. Children also had the opportunity to generalize these skills through social skills groups. Children were also taught additional strategies for communication and social interaction in the groups using techniques including posters, modelling, role plays, and group discussions. Social skills groups initially formed half of the intervention session and immediately followed computer game sessions with proportion of intervention components gradually altered to 37.5% computer game and 62.5% social skills groups in the last intervention sessions. Running concurrently with the child intervention, there was also a parent training component designed to help parents understand what their child was learning and teach them how to support generalization. Homework assignments for the children were also part of the programme. No intervention for controls as they were assigned to a waitlist. **Delivery of intervention:** Children received the intervention in groups of three. Therapists were interns enrolled in post-graduate clinical psychology and counselling degrees. **Format or method of administration:** Group. **Intensity:** 2 hours a week for 7 weeks followed by 1 hour in the final week. A total of 15 hours. Make-up sessions were offered to children who missed

	sessions. Actual number of hours completed by participants was not reported. **Duration of intervention:** 7 weeks **Total duration of follow-up:** 22 weeks (including 6-week and 5-month follow-ups but control data only available for post-intervention, as following this, the control group began the intervention)
Outcomes	**Direct Outcome:** **Core autism feature: Impaired reciprocal social communication and interaction** (as measured by the Social Skills Questionnaire [SSQ], Emotion Regulation and Social Skills Questionnaire [ERSSQ; a social skills measure designed for this study], the Assessment of Perception of Emotion from Facial Expression [Spence, 1995], the Assessment of Perception of Emotion from Posture Cues [Spence, 1995], James and the Maths Test [Attwood, 2004] and Dylan is Being Teased [Attwood, 2004].
Study Design	RCT
Source of funding	Not reported in the paper
Limitations	1. Unknown risk of selection bias: randomisation method was not reported. 2. High risk of performance bias: neither participants nor care administrators were blind 3. Risk of detection bias is different for different outcomes: SSQ - high risk as parent rated and parents participated in intervention; Assessment of Perception of Emotion from Facial Expression - unclear risk as rater not reported; Assessment of Perception of Emotion from Posture Cues - unclear risk as rater not reported; Dylan is Being Teased - unclear risk as blind double-coding was only performed for 33% of responses and scoring was performed by the chief investigator; James and the Maths Test - unclear risk as blind double-coding was only performed for 33% of responses and scoring was performed by the chief investigator; ERSSQ - high risk as questionnaire designed specifically for this study with no independent ratings of reliability or validity and parent-rated and parents participated in the intervention 4. Unclear risk of selective outcomes bias: all data were reported, but the study was not registered 5. High risk of other bias: potential conflict of interest as lead researcher developed the programme and is in the process of having it disseminated
Notes	Not applicable

1.1.4 BEGEER2011

Study ID	BEGEER2011
Bibliographic reference	Begeer S, Gevers C, Clifford P, Verhoeve M, Kat K, Hoddenbach E, et al. Theory of mind training in children with autism: a randomized controlled trial. Journal of Autism and Developmental Disorders. 2011;41:997-1006.
Methods	**Allocation:** Randomised **Matching:** No matching **Blindness:** Unclear - no blinding of participants, care administrators or outcome assessors reported **Setting:** Not reported **Raters:** Clinicians and parents **Country:** Holland
Participants	**Diagnosis:** DSM-IV-TR Autism Spectrum Disorder (Autism, Asperger Syndrome and Pervasive Developmental Disorder not otherwise specified) **Coexisting conditions:** None reported **Qualifying Diagnostic Assessment:** Clinical interview (no further details reported) **N:** 40 **Age:** Range: 8.25-13.6 years (Mean: 10.3) **Sex:** 8% female **Ethnicity:** Not reported **IQ:** Range 79-133 (Mean: 101.6) WISC-III Short-form **Inclusion criteria:** Children were included if they had: a DSM-IV-TR Autism Spectrum Disorder diagnosis and a WISC-III IQ of 70 or above. **Exclusion criteria:** None reported
Interventions	**Experimental Intervention: Theory of Mind training.** Children were taught in similar aged groups (age difference <3 years) about theory of mind and social skills such as listening to others, making friends, perception and imitation, fantasy-reality difference, assessing social situations, emotion recognition, first- and second-order mental state reasoning, deception, imagination and humour. Approach was manualized (Gevers et al., 2006; Steerneman et al., 1996). Intervention also involved concurrent parent information/training sessions to promote generalization including parents joining children for the last 15 minutes of every session to be informed about content covered and briefed about assignments for next session and monthly training sessions where parents were given suggestions on how to promote social cognition at home **Delivery of intervention:** Received intervention in groups of five or six, delivered by certified therapists. **Format or method of administration:** Group. **Intensity:** One 1.5 hr session a week for 16 weeks. A total of 24 hours. **Duration of intervention:** 16 weeks. **Total duration of follow-up:** 16 weeks
Outcomes	**Direct Outcome:** **Core autism feature: Impaired reciprocal social communication and interaction** (as measured by the Theory of Mind test [ToM], Levels of Emotional Awareness Scale for Children [LEAS-C), Index of Empathy for Children and Adolescents and Children's Social Behavior Questionnaire [CSBQ].

Study Design	RCT
Source of funding	Not reported
Limitations	1. Unknown risk of selection bias: An independent researcher made the allocation schedule, but methods of randomisation and concealment of allocation have not been reported. 2. High risk of performance bias: care for the control group has not been reported and participants and care administrators were not blinded as participants were either assigned to the intervention or a waiting-list control group 3. Risk of detection bias different for different outcomes: ToM - uncelar risk as no blinding of outcome assessors reported; LEAS-C - unclear risk as no blinding of outcome assessors reported; Index of Empathy for Children and Adolescents - high risk as participant rated and no blinding of children reported; CSBQ - high risk as parent rated and parents were not blind to treatment allocation 4. Unknown risk for selective reporting bias: all outcomes are reported, but the study has not been registered.
Notes	Not applicable

1.1.5 CARTER2011

Study ID	CARTER2011
Bibliographic reference	Carter AS, Messinger DS, Stone WL, Celimli S, Nahmias AS, Yoder P. A randomized controlled trial of Hanen's 'more than words' in toddlers with early autism symptoms. Journal of Child Psychology and Psychiatry. 2011;52:741-752.
Methods	**Allocation:** Randomised **Matching:** No matching **Blindness:** Participants, parents and intervention administrators were non-blind. The outcome assessors for the Early Social Communication Scales (ESCS) were blinded. However, for other outcome measures there was either only a subsection (20%) of observations coded blind, or it was not clear who the outcome assessors were or whether they were blinded, or outcome measures were based on non-blind parent report/interview rather than direct behaviour observation **Setting:** Clinic and home **Raters:** Parent-report/interview or not reported **Country:** USA
Participants	**Diagnosis:** DSM-IV Autistic disorder or PDD-NOS **Coexisting conditions:** None reported **Qualifying Diagnostic Assessment:** Clinical impression of clinical psychologist that child met DSM-IV symptom criteria for autistic disorder or PDD-NOS based on the Screening Tool for Autism in Two-year-olds (STAT), other baseline outcome measures and in some cases information provided by the parents regarding observed symptoms and experiences of their child at home **N:** 62 **Age:** 1-2 years (mean: 1.8 years) **Sex:** Not reported **Ethnicity:** 47% white **IQ:** Not reported **Inclusion criteria:** Younger than 24 months of age and obtained a predetermined 'at-risk' score on the STAT and met symptom criteria for an ASD based on expert clinical impression **Exclusion criteria:** Participants were excluded if they had a coexisting genetic disorder
Interventions	**Experimental Intervention: Hanen's 'More than Words'.** The intervention involves group-based parent training and individualized in-home parent-child sessions and focuses on improving the child's social communication through teaching parents to use techniques including using joint action routines, using visual supports, supporting peer interactions, responding to the child's communicative attempts and following their lead, and using books and play to elicit and to reward communication. **Delivery of intervention:** The intervention was delivered by a speech/language pathologist certified by the Hanen Centre. Group size for the parent training is not reported **Format or method of administration:** Individual parent-child and group-based parent training **Intensity:** Hours of intervention not reported (intervention consisted of 8 group parent-training sessions and 3 individualized parent-child sessions)

	Duration of intervention: 15 weeks **Total duration of follow-up:** 39 weeks (with post-intervention assessments at 22 weeks and follow-up assessments at 39 weeks)
Outcomes	**Direct outcome:** **Core autism feature: Impaired reciprocal social communication and interaction** (as measured by the Early Social Communication Scales [EScs]: Initiating Joint Attention [IJA] and Initiating Behavioural Requests [IBR] subscales; the Autism Diagnostic Observation Schedule [ADOS/ADOS-G] - Communication & Social Interaction score; the Parent-Child Free Play Procedure [PCFP] - Frequency of intentional communication [weighted]; and the Parent Interview for Autism-Clinical Version [PIA-CV] - Nonverbal communication scale) **Indirect outcomes:** **Coexisting problems or disorders: Adaptive behaviour** (as measured by the Vineland Adaptive Behaviour Scale [VABS] - Socialization, Communication, and Daily Living Skills subscales); **Speech and language** (as measured by the Mullen Scales of Early Learning [MSEL] - Expressive Language Age [months] and Receptive Language Age [months]); **IQ** (as measured by the MSEL Early-learning composite score); and **fine and gross motor skills** (as measured by the MSEL Fine Motor Age [months] and the VABS Motor Skills subscale)
Study Design	RCT
Source of funding	Autism Speaks and the Marino Autism Research Institute
Limitations	1. Risk of selection bias is unclear/unknown as there is insufficient detail reported with regards to allocation concealment 2. High risk of performance bias as the intervention administrator is not blinded 3. High risk of response bias as the participants were not blinded 4. Risk of detection bias was different for different outcome measures but the risk was unclear/unknown for PCFP as only a subsection (20%) of observations were coded blind, for MSEL and ADOS as identity and blinding of outcome assessor not reported and for VABS as based on parental interview rather than direct behavioural observation. High risk of detection bias for PIA-CV as parent-completed and parents non-blind 5. Risk of selective reporting bias is unclear/unknown as the trial is not registered on ClinicalTrials.gov
Notes	Data entered into meta-analysis was for post-intervention assessments for the direct outcome measures rather than follow-up to be consistent with other studies in meta-analysis. For indirect outcomes the data entered into meta-analysis was for follow-up assessment as this was the only time point reported for these measures. Data was not extracted for PCFP proportion of codable intervals with parental responsivity as given that the intervention was caregiver-mediated this outcome measure was a fidelity measure rather than a measure of clinical efficacy.

1.1.6 DEROSIER2011

Study ID	DEROSIER2011
Bibliographic reference	DeRosier ME, Swick DC, Ornstein Davis N, Sturtz McMillen J, Matthews R. The efficacy of a social skills group intervention for improving social behaviors in children with high functioning autism spectrum disorders. Journal of Autism and Developmental Disorders. 2011;41:1033-1043.
Methods	**Allocation:** Randomised **Matching:** No matching **Blindness:** Non-blind **Setting:** Private community-based clinic **Raters:** Self-completed and parent-rated **Country:** USA
Participants	**Diagnosis:** Parent report of diagnosis: 42% high functioning autism, 38% Asperger's Disorder, and 16% PDD-NOS **Coexisting conditions:** None reported **Qualifying Diagnostic Assessment:** Parent report of a prior diagnosis and meet the cut-off on any one of three screeners: Social Communication Questionnaire (SCQ); High-Functioning Autism Spectrum Screening Questionnaire (ASSQ); Childhood Asperger Syndrome Test (CAST). **N:** 55 **Age:** Range not reported but inclusion criteria 8-12 years (mean: 10 years) **Sex:** 2% female **Ethnicity:** 93% white **IQ:** Not reported (but inclusion criteria IQ>=85) **Inclusion criteria:** Children had to be aged 8-12 years old, have a prior diagnosis of high functioning autism, Asperger's Disorder, or PDD-NOS (by parent report), meet the cut-off on one of the three screening questionnaires administered (SCQ; ASSQ; CAST); and have an IQ >=85 (based on parent report and WISC-IV VIQ>=85) **Exclusion criteria:** Children were excluded if they scored greater than a T score of 70 (the clinical cut-off) for the Aggressive scale of the Child Behavioral Checklist (CBCL)
Interventions	**Experimental Intervention: Social Skills Group Intervention - High Functioning Autism (SSGRIN-HFA)** An autism-specific adaptation of a standard social skills group intervention that used cognitive-behavioural and social learning techniques to build social skills and peer relationships. The specific adaptations included the progressive introduction of skills, a focus on socially relevant goals, varied learning opportunities, and structure and predictability. The intervention consisted of three modules: Communication (including verbal communication, non-verbal communication and listening skills); working with others (including consequences and stop and think, perspective taking, cooperation and compromise); and friendship skills (including making and keeping friends, initiation, social problem solving and coping with bullying and teasing. This adaptation also differed from standard social skills group intervention in that the involvement of the parents was greater, with parents of children in the experimental group attending an extra four sessions (orientation to the group, and review of each module) and involved through at-home practice **Control Intervention: Standard Social Skills Group Intervention (S.S.GRIN)** according to the treatment manual (DeRosier, 2007) developed to build social

	skills and peer relationships for typically developing children who were socially at-risk **Delivery of intervention:** Group size and who delivered the intervention not reported **Format or method of administration:** Group **Intensity:** 15 hours (1 hour per week) for experimental and 10 hours for control **Duration of intervention:** 15 weeks **Total duration of follow-up:** 19 weeks (15 weeks of intervention preceded by baseline assessments two weeks prior to intervention and post-intervention assessments within two weeks following the intervention)
Outcomes	**Direct outcome:** **Core autism feature: Impaired reciprocal social communication and interaction** (as measured by Social Responsiveness Scale [SRS] - Social Awareness, Social Cognition, Social Communication, Social Motivation, and Autistic Mannerisms [standardized change scores]; self-reported Social Self-efficacy Scale [standardized change score]; and Social Dissatisfaction Questionnaire [standardized change score])
Study Design	RCT
Source of funding	National Institute of Mental Health (NIMH), contract HHS-N-271-2006-64102-C
Limitations	1. High risk of selection bias as randomisation method is unclear and insufficient detail reported with regards to allocation concealment. There was also a statistically significant group difference at baseline with the experimental group showing higher scores on the Social Responsiveness Scale (SRS)-Social Communication domain relative to the control group (means of 69.6 and 66.0 respectively) 2. High risk of performance bias as the intervention administrator was non-blind 3. High risk of response bias as the participants were non-blind 4. High risk of detection bias as the outcome measures relied on non-blind self- or parent-report 5. Risk of selective reporting bias is unclear/unknown as the trial protocol is not registered on ClinicalTrials.gov.uk
Notes	Authors contacted for endpoint rather than change score data but no reply so change scores entered into meta-analysis. Downgraded on the basis of indirectness due to the population because there was no qualifying diagnostic assessment by a clinician

1.1.7 DREW2002

Study ID	DREW2002
Bibliographic reference	Drew A, Baird G, Baron CS, Cox A, Slonims V, Wheelwright S, et al. A pilot randomised control trial of a parent training intervention for pre-school children with autism. Preliminary findings and methodological challenges. European Child and Adolescent Psychiatry. 2002;11:266-272.
Methods	**Allocation:** Randomised **Matching:** No matching **Blindness:** Non-blind **Setting:** Home **Raters:** Parent- and clinician-completed **Country:** UK
Participants	**Diagnosis:** ICD-10 Childhood Autism **Coexisting conditions:** None reported **Qualifying Diagnostic Assessment:** Screening with a shortened version of the Checklist for Autism in Toddlers (CHAT), followed by full clinical assessment including administering the Autism Diagnostic Interview-Revised (ADI-R), a structured child-adult interaction assessment to elicit examples of social interaction, reciprocity, non-verbal social communication abilities and affective responsivity, and a consensus clinical diagnosis made by two clinicians based on all available clinical, historical and psychometric information **N:** 24 **Age:** Range not reported (mean: 1.9 years) **Sex:** 21% female **Ethnicity:** Not reported **IQ:** Range not reported (mean NVIQ: 77.1) **Inclusion criteria:** Children were included if they: were referred by a Health Visitor on the basis of failing all 6 items on a shortened version of the CHAT (lack of pointing for interest [parent and Health Visitor report]; lack of pointing for request [parent report]; lack of pretend play [parent and Health Visitor report]; failure to monitor gaze [Health Visitor report]) and there was a concern about possible autism; failed all 6 items on the CHAT when it was readministered over the telephone by a member of the research team; had a clinical diagnosis of childhood autism **Exclusion criteria:** Health Visitors were asked not to refer children with severe general developmental delay
Interventions	**Experimental Intervention: Parent training**. This intervention emphasized the development of joint attention and joint action routines, and included advice about behaviour management. Therapists described developmental principles and then monitored and provided feedback on parents' implementation. Parents were instructed on how to teach joint attention behaviours such as pointing and gaze switching, including the use of visual supports for spoken language and techniques were implemented in allocated times for activities (for instance, joint play times) but also integrated into everyday routines, such as mealtimes, dressing and bedtimes. Instruction in behaviour management techniques followed a similar structure and included instruction in the principles of reinforcement, interrupting unwanted behaviours and encouraging alternative behaviours through joint action routines. **Delivery of intervention:** Speech and language therapists delivered the intervention to parents in their homes

	Format or method of administration: Individual **Intensity:** Actual intensity not reported but planned intensity was 26 hours (3 hours/6 weeks, equating to 0.5 hours/week) **Duration of intervention:** 52 weeks **Total duration of follow-up:** 52 weeks
Outcomes	**Direct outcome:** **Core autism feature: Impaired reciprocal social communication and interaction** (as measured by the Autism Diagnostic Interview-Revised [ADI-R] - Reciprocal Social Interaction and Nonverbal Communication domains) **Indirect outcomes:** **Core autism feature: Restricted interests and rigid and repetitive behaviours** (as measured by ADI-R - Repetitive and Stereotyped Behaviour domain) **Coexisting problems or disorders: IQ** (as measured by Griffiths Scale of Mental Development: D and E scales [NVIQ NVMA/age]); and **Speech and language** (as measured by the MacArthur Communication Developmental Inventories [CDI]- Words understood, Words said and Total gestures produced; and dichotomous measures of overall language rating based on ADI-R of non-verbal [<5 words], single words or phrase speech) **Impact on family: Parental stress** (as measured by Parental Stress Inventory - Total score)
Study Design	RCT
Source of funding	Medical Research Council Project Grant and a grant from the Special Trustees of Guy's Hospital to Simon Baron-Cohen, Antony Cox and Gillian Baird supported this research
Limitations	1. High risk of selection bias due to a statistically significant baseline difference between groups (the experimental group had a higher NVIQ than the control group, 88.1 compared to 66, $p<0.001$) and there was insufficient detail reported with regards to allocation concealment 2. High risk of performance bias as the intervention administrators were non-blind and there is evidence for a potential care confound as three participants in the control group (25%) commenced an EIBI program during the intervention period and there was a trend for a statistically significant difference in the number of hours of other intervention with the control group receiving 8.4 hours and the experimental group receiving 0.3 hours ($p=0.07$) 3. High risk of response bias as the participants were non-blind 4. High risk of detection bias as outcome assessors were non-blind 5. Risk of selective reporting bias is unclear/unknown as the trial protocol is not registered on ClinicalTrials.gov or ISRCTN
Notes	Not applicable

1.1.8 FRANKEL2010

Study ID	FRANKEL2010
Bibliographic reference	Frankel F, Myatt R, Sugar C, Whitham C, Gorospe CM, Laugeson E. A randomized controlled study of parent-assisted children's friendship training with children having autism spectrum disorders. Journal of Autism and Developmental Disorders. 2010;40:827-842.
Methods	**Allocation:** Randomised **Matching:** No matching **Blindness:** Non-blind **Setting:** Outpatient **Raters:** Self-, parent- and teacher-report **Country:** USA
Participants	**Diagnosis:** Autism Spectrum Disorder (ASD) **Coexisting conditions:** None reported **Qualifying Diagnostic Assessment:** Children had to score >21 on the High Functioning Autism Spectrum Screening Questionnaire (ASSQ) and meet criteria for ASD on the Autism Diagnostic Interview-Revised (ADI-R) and the Autism Diagnostic Observation Schedule-Generic (ADOS-G) **N:** 76 (N=76 randomised but demographic and efficacy data reported for N=68) **Age:** Range not reported but inclusion criteria 7-11 years (mean: 8.5 years) **Sex:** 15% female **Ethnicity:** 66% white **IQ:** Range not reported (mean WISC-III VIQ: 103.8) **Inclusion criteria:** Children needed to: score >21 points on the ASSQ; meet ADOS-G and ADI-R criteria for ASD; currently attend a 2nd-5th grade regular classroom for most of the school day without a closely supervising adult; have a VIQ>60; demonstrate a capacity for joint attention and basic social reciprocity, as measured by an ability to switch topics in a conversation when the other person was interested in talking about something else; and have sufficient play repertoire to engage with other children on play dates, as measured by adequate knowledge of rules in playing at least two common age-appropriate board games and common school yard games **Exclusion criteria:** Children were excluded if they: were currently prescribed any psychotropic medication; had a thought disorder; or had clinical seizure disorder, gross neurologic disease, or other medical disorder such as moderately impaired hearing or severe uncorrectable visual impairment
Interventions	**Experimental Intervention: Parent-assisted Children's Friendship Training (CFT).** Group-based social skills intervention with individuals with autism integrated into a mixed clinical group (18.6% Adjustment Disorder, 46% ADHD, 2.7% ADHD and ODD, 0.5% ODD alone, 0.7% Fetal Alcohol Spectrum Disorder, 4.9% anxiety disorder, 1.3% mood disorder, 1.3% LD and 25.2% no diagnosis). Children and parents were seen at the same time in separate sessions. Children were taught social skills in terms of rule-based procedures using techniques including instruction, modelling, rehearsal and performance feedback. Homework assignments were also used to try and increase generalization, including calling another member of the class, parent-supported play dates, and practicing "making fun of the teasing" with a child who was teasing them. The sessions for children followed a specified structure with 10 minutes dedicated to reviewing homework assignments, 20 minutes

	consisting of a didactic presentation and coached behavioural rehearsal between children, and 25 minutes of coached play in which children practiced newly learned skills and in the final 5 minutes parents and children reunited to finalize contracts for homework. Parent sessions consisted of orientation, review of previous socialization homework assignment, and discussion of potential problems for the next homework assignment. **Delivery of intervention:** Intervention was delivered to groups of around 10 children, with no more than 4 children with ASD in any one group. The child intervention was delivered by a PhD level psychologist (one of the investigators) and the parent intervention was delivered by a licensed clinical social worker (another of the investigators) **Format or method of administration:** Group **Intensity:** Range of hours of actual/attended intervention not reported (mean: 11.3 hours) **Duration of intervention:** 12 weeks **Total duration of follow-up:** 24 weeks (including 12 week post-intervention follow-up for the experimental group and 12-week intervention for the waitlist control group)
Outcomes	**Direct outcome:** **Core autism feature: Impaired reciprocal social communication and interaction** (as measured by Loneliness Scale; Piers-Harris Self-Concept Scale [PHS] - Popularity subscale; Quality of Play Questionnaire [QPQ] - Guest, Engage and Disengage subscales; Social Skills Rating System [SSRS] - Assertion subscale) **Indirect outcomes:** **Coexisting problem or disorder: Adaptive behaviour** (as measured by the SSRS - Self-control subscale) **Behaviour that challenges** (as measured by the SSRS - Externalizing and Internalizing subscales; QPQ Conflict subscale; and Pupil Evaluation Inventory [PEI] - Withdrawal and Aggression subscales)
Study Design	RCT
Source of funding	NIH Research Grant U54 MH68172 funded by the National Institute of Mental Health, NICHD, NIDCD and NINDS, Marian Sigman, STAART Center Program Principal Investigator and Fred Frankel, Project Principal Investigator
Limitations	1. Risk of selection bias is unclear/unknown due to insufficient detail reported with regards to allocation concealment 2. High risk of performance bias as the intervention administrator was non-blind 3. High risk of response bias as participants were non-blind 4. High risk of detection bias as outcome measures were based on non-blind parent-, self- or teacher-report and some of the scales had not been validated in an ASD population 5. High risk of attrition bias due to a greater drop-out rate in the experimental (N=14; 35%) than in the control (N=5; 14%) 6. Risk of selective reporting bias is unclear/unknown as the trial protocol is not registered on ClinicalTrials.gov
Notes	Data were not extracted for QPQ Host as given that the intervention was parent-assisted and this outcome measure relied on parental assistance in order to set up a play date it was a fidelity measure rather than a measure of clinical efficacy

1.1.9 GOLAN2010

Study ID	GOLAN2010
Bibliographic reference	Golan O, Ashwin E, Granader Y, McClintock S, Day K, Leggett V, et al. Enhancing emotion recognition in children with autism spectrum conditions: an intervention using animated vehicles with real emotional faces. Journal of Autism and Developmental Disorders. 2010;40:269-279.
Methods	**Allocation:** Randomised **Matching:** Matched on sex, age and verbal ability **Blindness:** No blinding of participants, individuals responsible for administering care or outcome assessors reported **Setting:** Home **Raters:** Investigator **Country:** UK
Participants	**Diagnosis:** DSM-IV Autism Spectrum Disorder **Coexisting conditions:** None reported **Qualifying Diagnostic Assessment:** Autism Diagnostic Interview-Revised (ADI-R) and Childhood Asperger Syndrome Test (CAST) **N:** 39 **Age:** Range: 4-8 years (Mean: 5.9) **Sex:** 26% female **Ethnicity:** Not reported **IQ:** VIQ 76-116 (mean: 98.8; as measured by British Picture Vocabulary Scale [BPVS-2nd ed.]) **Inclusion criteria:** Not reported **Exclusion criteria:** Not reported
Interventions	**Experimental Intervention: The Transporters emotion recognition training.** The intervention group were provided with an animated Transporters DVD to take home and watch a minimum of three episodes a day. The DVD was a 3D animation series featuring eight vehicle characters with real human faces grafted on to them, designed to enhance the understanding and recognition of emotions by children with autism aged 3-8 years old. The DVD included fifteen 5-minute episodes which each focused on a key emotion or mental state (happy, sad, angry, afraid, disgusted, surprised, excited, tired, unfriendly, kind, sorry, proud, jealous, joking and ashamed). The DVD also included a selection of quizzes that relate to each episode where children were required to match faces to faces, faces to emotions, and situations to faces. Parents and carers were also given a detailed guide to the DVD so that they could supervise and facilitate their child watching and learning. Delivery of intervention: The intervention was delivered individually in the home, via an animated DVD. **Format or method of administration:** Individual **Intensity:** The planned intensity was for children to watch a minimum of three, five-minute episodes every day for four weeks. A minimum of 7 hours (1.75 hours per week). Actual intensity not reported **Duration of intervention:** 4 weeks **Total duration of follow-up:** 4 weeks
Outcomes	**Direct Outcome:** **Core autism feature: Impaired reciprocal social communication and interaction, relating to emotion recognition** (as measured by Emotional

	Vocabulary [EmoVoc] and Situation-Facial Expression Matching [SEM] - Familiar close generalization, Unfamiliar close generalization and Distant generalization levels)
Study Design	RCT
Source of funding	Department for Culture, Media and Sport (DCMS)
Limitations	1. Unknown risk of selection bias: Methods of randomisation and concealment allocation have not been reported. 2. High risk of performance bias: blinding of care administrators has not been reported and participants were not blind as they were either assigned to the intervention or a no-treatment control group. 3. High risk of detection bias: Outcomes rated by non-blind investigator and no independent measures of reliability or validity for any measures 4. Unknown risk for selective reporting bias: all outcomes are reported, but the study has not been registered. 5. Hign risk of detection bias as outcomes were rated by a non-blind investigator and there were no independent measures of reliability or validity
Notes	The results of the SEM level 3 have been combined with the emotion recognition meta-analysis

1.1.10 GREEN2010

Study ID	GREEN2010
Bibliographic reference	Green J, Charman T, McConachie H, Aldred C, Slonims V, Howlin P, et al. Parent-mediated communication-focused treatment in children with autism (PACT): a randomised controlled trial. Lancet. 2010;375:2152-2160.
Methods	**Allocation:** Randomised **Matching:** Probablilistic minimisation of imbalance in the marginal distribution of treatment centre, age and autism severity **Blindness:** Outcome assessors were blinded. However, intervention administrators, participants and parents were non-blind **Setting:** Outpatient **Raters:** Clinician-rated and parent-report **Country:** UK
Participants	**Diagnosis:** ADOS-G & ADI-R Core Autism **Coexisting conditions:** None reported **Qualifying Diagnostic Assessment:** Autism Diagnostic Observation Schedule-Generic (ADOS-G) and Autism Diagnostic Interview-Revised (ADI-R) **N:** 152 **Age:** 2-5 years (mean: 3.8 years) **Sex:** 9% female **Ethnicity:** 57% white **IQ:** Range not reported (mean Mullen Scales of Early Learning [MSEL]: Non-verbal IQ age equivalent: 26.2 months) **Inclusion criteria:** Children needed to be aged 2-4.9 years and meet the criteria for core autism on the ADOS-G (social and communication domains) and the ADI-R (two of the three domains) **Exclusion criteria:** Children were excluded if they had: a twin with autism; a non-verbal age equivalent<12 months on the Mullen Early Learning Scales; epilepsy requiring medication; a severe hearing or visual impairment or if their parent did; or a parent with a severe psychiatric disorder requiring treatment
Interventions	**Experimental Intervention: Parent-mediated communication-focused treatment (PACT).** PACT consisted of one-to-one clinic sessions between therapist and parent (with the child present) and used techniques such as video feedback to increase parental sensitivity and responsiveness to child communication. Strategies such as joint action routines, familiar repetitive language and pauses were also encouraged in order to develop the child's communication **Delivery of intervention:** Speech and language therapists delivered the intervention **Format or method of administration:** Individual **Intensity:** IQR 26-34 hours (mean: 28 hours) **Duration of intervention:** 56 weeks **Total duration of follow-up:** 56 weeks
Outcomes	**Direct outcome:** **Core autism feature: Impaired reciprocal social communication and interaction** (as measured by Autism Diagnostic Observation Schedule-Generic [ADOS-G] - Communication & Social Interaction, Communication, and Social

	Interaction; and behavioural observation of parent-child interactions - child initiations [%] and shared attention time [%]; and the Communication and Symbolic Behavior Scales Developmental Profile [CSBS DP] - Social composite) **Indirect outcomes:** **Core autism feature: Restricted interests and rigid and repetitive behaviours** (as measured by the ADOS-G - Repetive Behaviours domain) **Coexisting problems or disorders: Adaptive behaviour** (as measured by Vineland Adaptive Behaviour Scale [VABS] - Communication subscale and adaptive behaviour composite score); **Speech and language** (as measured by the Preschool Language Scale-3 [PLS-3] - Auditory Comprehension and Expressive Communication; and the MacArthur Communication Developmental Inventories [CDI] - Vocabulary Comprehension and Vocabulary Production)
Study Design	RCT
Source of funding	This study was sponsored by the University of Manchester. PACT was funded by the Medical Research Council (G0401546), the UK Department for Children, Schools and Families; with a UK Department of Health award for excess treatment and support costs
Limitations	1. Risk of selection bias is unclear/unknown as there was a significant group difference at baseline (socioeconomic status and proportion of parents with qualifications gained after age 16 years were higher in the experimental than in the control group with cohen's d effect sizes of 0.14 and 0.48 respectively) 2. High risk of performance bias as intervention administrators were non-blind 3. High risk of response bias as participants were non-blind 4. Risk of detection bias is different for different outcomes and is high risk for CSBS-DP and CDI as parent-reported and parents were non-blind and involved in the intervention and the risk of detection bias is unclear/unknown for VABS as teacher-rated and unclear if teacher blinded
Notes	This trial was registered on ISRCTN, Study ISRCTN58133827. Data was not extracted for parental synchrony as given that the intervention was caregiver-mediated this outcome measure was a fidelity measure rather than a measure of clinical efficacy.

1.1.11 HOPKINS2011

Study ID	HOPKINS2011
Bibliographic reference	Hopkins IM, Gower MW, Perez TA, Smith DS, Amthor FR, Wimsatt FC, et al. Avatar assistant: improving social skills in students with an ASD through a computer-based intervention. Journal of Autism and Developmental Disorders. 2011;41:1543-1555.
Methods	**Allocation:** Randomised **Matching:** No matching **Blindness:** Research assistants conducting observations and parents were blind to group allocation, but blindness of investigators is not reported **Setting:** Educational (school or after-school club) **Raters:** Parents and research assistants on two measures, but raters are not reported for all measures. **Country:** USA
Participants	**Diagnosis:** DSM-IV Autism Spectrum Disorder **Coexisting conditions:** Not reported **Qualifying Diagnostic Assessment:** CARS (Childhood Autism Rating Scale) **N:** 51 **Age:** Range: 6.25-15 years (Mean: 10.17 years) **Sex:** 10% female **Ethnicity:** 71% white **IQ:** Range not reported (Mean:75.71) Kaufman Brief Intelligence Test - Second Edition (KBIT-2) **Inclusion criteria:** A previous DSM-IV diagnosis of ASD by a licensed community professional. **Exclusion criteria:** Not reported
Interventions	**Experimental Intervention: FaceSay.** FaceSay is a computer-based program which used interactive avatars (animated photographs of real people) to teach children social skills, including joint attention skills, holistic facial processing and face recognition and emotion recognition skills. Program activities included eye gaze following, matching and manipulating facial expressions and completing face puzzles. **Control Intervention: Attention-placebo condition.** Participants in the control group used a drawing software program (Tux Paint) **Delivery of intervention:** The intervention was delivered to each child individually via a computer programme, with the support of one or two of the investigators **Format or method of administration:** Individual **Intensity:** Actual intensity not reported but planned intensity was 2-5 hours (0.3-0.8 hour/week) **Duration of intervention:** 6 weeks **Total duration of follow-up:** 8 weeks (post-intervention measures were collected within 2 weeks of the final intervention session)
Outcomes	**Direct Outcome:** **Core autism feature: Impaired reciprocal social communication and interaction, relating to emotion recognition** (as measured by Ekman emotion recognition photographs, a study-specific emotion recognition in drawings test, the Benton Facial Recognition Test [Benton, 1980], Social Skills Rating System [SSRS] and a behavioural observation).

Study Design	RCT
Source of funding	This study was funded in part by a grant from Civitan International. No further information reported.
Limitations	1. Unknown risk of selection bias: Methods of randomisation and concealment of allocation have not been reported 2. Unknown risk of performance bias: Details of care provided to the two groups are not reported and no blinding is reported for the investigators, but participants were blind to their allocation as there was an intervention group and an attention-placebo condition. 3. Risk of detection bias different for different measures: Ekman emotion recognition photographs - unclear; Benton Facial Recognition long-form - high risk; Benton Facial Recognition short-form - unknown risk; SSRS - unknown risk; behavioural observation - low risk 4. Unknown risk for selective reporting bias: all outcomes are reported, but the study has not been registered
Notes	The investigators had a pre-determined attendance cut-off of 83%. Two participants are reported to have been excluded from the study for not meeting this cut off, but it is not reported which groups these participants had been allocated to. Where there were no significant differences between the IQ <70 and IQ >70 groups, the results have been combined for the analysis

1.1.12INGERSOLL2012

Study ID	INGERSOLL2012
Bibliographic reference	Ingersoll B. Brief report: effect of a focused imitation intervention on social functioning in children with autism. Journal of Autism and Developmental Disorders. 2012;42:1768-1773.
Methods	**Allocation:** Randomised **Matching:** Matched on expressive language age (as measured by the Preschool Language Scale, 4th Edition [PLS-4]) **Blindness:** Non-blind **Setting:** Not reported **Raters:** Clinician and parent-report **Country:** USA
Participants	**Diagnosis:** DSM-IV-TR autistic disorder **Coexisting conditions:** Not reported **Qualifying Diagnostic Assessment:** Children received a clinical diagnosis based on DSM-IV-TR criteria from a licensed psychologist and met the cut-off for autism or ASD on the Autism Diagnostic Observation Schedule-Generic (ADOS-G) **N:** 29 **Age:** 2.3-3.9 years (mean: 3.2 years) **Sex:** 11% female **Ethnicity:** 63% white **IQ:** Not reported **Inclusion criteria:** Not reported **Exclusion criteria:** Not reported
Interventions	**Experimental Intervention: Reciprocal Imitation Training (RIT)** uses naturalistic techniques to teach imitation during social interaction. Techniques included contingent imitation, description of child actions using simplified language, expanding child utterances, modeling, verbal markers to describe actions, and physical prompting. **Delivery of intervention:** Therapists were undergraduate and graduate-level research assistants and each child worked with at least three different therapists throughout treatment to promote generalization. **Format or method of administration:** Individual **Intensity:** 3 hours per week, total of 30 hours of intervention **Duration of intervention:** 10 weeks **Total duration of follow-up:** 23 weeks (including 2-3 month follow-up)
Outcomes	**Direct outcome:** **Core autism feature: Impaired reciprocal social communication and interaction** (as measured by the EScs [Early Social Communication Scales] - Initiating Joint Attention subscale and the Bayley Scales of Infant Development - Social-Emotional subscale)
Study Design	RCT
Source of funding	Not reported
Limitations	1. Risk of selection bias is unclear/unknown as insufficient detail reported with regards to allocation concealment 2. High risk of response bias as participants were not blind to group assignment

	3. High risk of performance bias as intervention administrators were not blind to group assignment 4. High risk of detection bias as outcome assessors were not blind to group assignment 5. Risk of selective reporting bias is unclear/unknown as the trial protocol is not registered
Notes	Data could not be extracted from the published paper. However, mean and standard deviation scores were requested and supplied by the author.

1.1.13 JOCELYN1998

Study ID	JOCELYN1998
Bibliographic reference	Jocelyn LJ, Casiro OG, Beattie D, Bow J, Kneisz J. Treatment of children with autism: a randomized controlled trial to evaluate a caregiver-based intervention program in community day-care centers. Journal of Developmental and Behavioral Pediatrics. 1998;19:326-334.
Methods	**Allocation:** Randomised **Matching:** Stratified based on autism severity (mild-moderate defined as CARS scores <=37 or severe defined as CARS scores >37) **Blindness:** Participants, parents and intervention administrators were non-blind but most outcome assessments were performed by blinded psychologist **Setting:** Outpatient, educational (day care centre) and home-based **Raters:** Parent-completed or psychologist who was blind to group assignment **Country:** Canada
Participants	**Diagnosis:** DSM-III-R pervasive developmental disorder or autism **Coexisting conditions:** None reported **Qualifying Diagnostic Assessment:** Recent diagnosis made by a developmental pediatrician **N:** 36 (N=36 randomised but demographic and efficacy data reported for N=35 completers) **Age:** Range not reported but inclusion criteria 2-6 years (mean: 3.6 years) **Sex:** 3% female **Ethnicity:** 94% white **IQ:** Range not reported (mean PIQ: 63.1) **Inclusion criteria:** Children were included if they: had a recent diagnosis of pervasive developmental disorder or autism; were aged 2-6 years old; lived within 60 miles of the city of Winnipeg **Exclusion criteria:** Children were excluded if they: were attending day care or school at the time of diagnosis; had a severe physical disability that would preclude completion of developmental test items
Interventions	**Experimental Intervention: Parent and day-care staff training:** Children attended community day care with the additional intervention of training for their parents and day-care staff. Parents and child care workers were taught how to: perform a functional analysis of behaviour; plan and evaluate strategies for changing behaviour; proactively facilitate language and social development to try and anticipate and avoid the development of problem behaviours. The intervention was delivered through hospital-based educational seminars (covering an introduction to autism, behaviour analysis techniques, interventions aimed at communication, techniques to improve social interaction and engage the child in play, and problem solving); on-site consultations to day care centres (conducted in parallel with seminars to facilitate practical application of techniques); and psychoeducational and supportive work with the family (including review meetings at the day care centre with the parents, and home visits to parents where written information about autism was provided, parents were given the opportunity to discuss concerns and questions, expectations and goals for the child were discussed, and videotapes of the child at daycare were reviewed to share intervention strategies and techniques) **Control Intervention: Standard day care**

	Delivery of intervention: Group size for educational seminars and individual/s administering the intervention were not reported **Format or method of administration:** Individual and group **Intensity:** Actual intensity not reported but planned intensity 50 hours (3 hours/week of educational seminars for 5 weeks and 3 hours/week of on-site day-care staff consultation for 10 weeks, and three parent-staff review meetings at day care centre [estimated at 3 hours] and 2 in-home visits [estimated at 2 hours]; equating to 4 hours/week) **Duration of intervention:** 12 weeks **Total duration of follow-up:** 12 weeks
Outcomes	**Direct outcome:** **Core autism feature: Overall autistic behaviours** (as measured by Autism Behaviour Checklist [ABC] - Total score) **Indirect outcomes:** **Coexisting problems or disorders: Adaptive behaviour** (as measured by Early Intervention Developmental Profile [EIDP]/Preschool Developmental Profile [PSDP] - Self-Care subscale); **Speech and language** (as measured by EIDP/PSDP - Language subscale); and **Fine and gross motor skills** (as measured by the EIDP/PSDP - Perceptual/Fine Motor and Gross Motor subscales) **Impact on family** (as measured by the Stress-Arousal Checklist - Mothers' Stress, Mothers' Arousal, Fathers' Stress and Fathers' Arousal subscales)
Study Design	RCT
Source of funding	Grant #6607-1649-62 from the National Health Research and Development Program (NHRDP)
Limitations	1. Risk of selection bias is unclear/unknown as there was a higher percentage of single parents in the control group (p=0.047) 2. High risk of performance bias as intervention administrators were non-blind 3. High risk of response bias as participants were non-blind 4. Risk of selective reporting bias is unclear/unknown as the trial protocol is not registered on ClinicalTrials.gov or ISRCTN
Notes	Not applicable

1.1.14 KAALE2012

Study ID	KAALE2012
Bibliographic reference	Kaale A, Smith L, Sponheim E. A randomized controlled trial of preschool-based joint attention intervention for children with autism. Journal of Child Psychology and Psychiatry. 2012;53:97-105.
Methods	**Allocation:** Randomised **Matching:** Blocked randomisation by study site **Blindness:** Outcome assessors were blinded. However, intervention administrators, participants and parents were non-blind **Setting:** Educational (preschool) **Raters:** Research assistants blind to study purpose, group allocation and testing order **Country:** Norway
Participants	**Diagnosis:** ICD-10 Childhood autism **Coexisting conditions:** None reported **Qualifying Diagnostic Assessment:** ICD-10 diagnosis was made by multi-disciplinary child and adolescent mental health clinic team based on a comprehensive clinical evaluation including testing with the Autism Diagnostic Observation Schedule (ADOS) and/or the Autism Diagnostic Interview-Revised (ADI-R) for 80% of sample **N:** 61 **Age:** Range not reported but inclusion criteria 2-5 years (mean: 4.1 years) **Sex:** 21% female **Ethnicity:** Not reported **IQ:** Range not reported (mean developmental quotient based on Mullen Scale of Early Learning [MSEL]: 56.2) **Inclusion criteria:** Children needed to be aged 2-5 years, have a confirmed ICD-10 diagnosis of childhood autism and attend a preschool **Exclusion criteria:** Children were excluded if they had a central nervous system disorder (such as epilepsy or cerebral palsy) or if their parents did not speak Norwegian
Interventions	**Experimental Intervention: Preschool-based joint attention training** which modified the joint attention intervention manual developed by Kasari (Kasari, 2006). The intervention was aimed at increasing child initiation of higher order joint attention (show, point, give) and encouraged joint attention initiation using techniques such as interesting toys, hiding the toys, prompting and modelling. **Delivery of intervention:** Intervention was delivered in a separate room in the preschool by preschool teachers involved in the children's regular preschool program **Format or method of administration:** Individual **Intensity:** Range not reported (mean: 25 hours) **Duration of intervention:** 8 weeks **Total duration of follow-up:** 8 weeks
Outcomes	**Direct outcome:** **Core autism feature: Impaired reciprocal social communication and interaction** (as measured by Early Social Communication Scales [EScs] - Initiating Joint Attention [IJA]; Preschool teacher-child play - Joint attention and Joint engagement; and mother-child play - joint attention and joint

	engagement)
Study Design	RCT
Source of funding	South-Eastern Norway Regional Health Authority, and Centre for Child and Adolescent Mental Health, Eastern and Southern Norway
Limitations	1. Risk of selection bias is unclear/unknown as the randomisation was blocked and so not truly random and there was a statistically significant group difference at baseline with the experimental group showing a lower expressive language age than the control group (18.8 relative to 24.9 months, p=0.047) 2. High risk of performance bias as the intervention administrators were non-blind 3. High risk of response bias as the participants were non-blind
Notes	

1.1.15 KASARI2006&2008/LAWTON2012

Study ID	KASARI2006&2008/LAWTON2012
Bibliographic reference	Kasari C, Freeman S, Paparella T. Joint attention and symbolic play in young children with autism: a randomized controlled intervention study. Journal of Child Psychology and Psychiatry. 2006;47:611-620. Kasari C, Paparella T, Freeman, S, Jahromi LB. Language outcome in autism: randomized comparison of joint attention and play interventions. Journal of Consulting and Clinical Psychology. 2008;76:125-137. Lawton K, Kasari C. Brief report: longitudinal improvements in the quality of joint attention in preschool children with autism. Journal of Autism and Developmental Disorders. 2012;42:307-312.
Methods	**Allocation:** Randomised **Matching:** No matching **Blindness:** Assessors were blind but intervention administrators, parents and participants were non-blind **Setting:** Outpatient **Raters:** Independent clinical testers (not associated with research staff and blind to study purpose and hypotheses) **Country:** USA
Participants	**Diagnosis:** Autism **Coexisting conditions:** None reported **Qualifying Diagnostic Assessment:** Clinical diagnosis of autism which was corroborated by the Autism Diagnostic Iinterview-Revised (ADI-R) and the Autism Diagnostic Observation Schedule (ADOS) **N:** 37 (data not extracted for symbolic play arm) **Age:** Range not reported but inclusion criteria was 3-4 years (mean: 3.6 years) **Sex:** 19% female **Ethnicity:** 70% white **IQ:** Range not reported (mean: 55.4) **Inclusion criteria:** Children were included if they: were currently attending an Early Intensive Behavioural Intervention (EIBI) preschool program; were aged 3-4 years; and had a clinical diagnosis of autism which was corroborated by the ADI-R and ADOS **Exclusion criteria:** Children were excluded if they: had seizures; had additional medical diagnoses (such as, genetic syndromes), were geographically inaccessible for follow-up visits; or planned to leave the EIBI preschool program in less than 4 weeks
Interventions	**Three-armed trial but data not extracted for the symbolic play arm:** **Combined joint attention training and EIBI:** Children who were already enrolled in an EIBI preschool program were given an additional joint attention training intervention. This intervention was aimed at increasing joint attention initiation (including coordinated joint looking, showing, giving to share, proximal and distal pointing) and responding to joint attention attempts (including following proximal and distal points). Each session of the joint attention intervention followed the same format with 5 minutes of a direct-instruction table activity where principles of applied behaviour analysis were used to prime the appropriate joint attention response using techniques such as positive reinforcement and hierarchical prompting (verbal prompt, model,

	physical prompt). The following 20 minutes of the session involved a move to naturalistic milieu instruction on the floor where the same goal was targeted but this time instruction was more child-driven and included techniques such as following the child's lead and interest in activities, talking about what the child was doing, repeating back and expanding child utterances, giving corrective feedback, sitting close to and making eye-contact with the child, and making environmental adjustments to engage the child. **EIBI only:** All participants in the study were already participating in an EIBI preschool program which was based on applied behaviour analysis principles and followed a typical preschool curriculum but with staff to participant ratios of 1:1 for 6 hours a day. Joint attention or symbolic play skills were not taught as a standard part of this EIBI. Staff in the EIBI program were independent of the research staff and blind to the hypotheses of the intervention study **Delivery of intervention:** Graduate students in educational psychology **Format or method of administration:** Individual **Intensity:** Combined joint attention training and EIBI: 14.3 hours (194.3 with added EIBI); EIBI only: 180 hours (30 hours/week) **Duration of intervention:** 5-6 weeks **Total duration of follow-up:** 52 weeks (there were two post-intervention follow-up assessments at 6 months and 1 year)
Outcomes	**Direct outcome:** **Core autism feature: Impaired reciprocal social communication and interaction** (as measured by Early Social Communication Scales [EScs] - Showing, Coordinated joint attention [JA] looks, Pointing, Giving, Responding to Joint Attention [RJA], JA & shared positive affect, and JA & shared positive affect & utterance); a behavioural observation of mother-child interaction (Coordinated Joint attention looks, Pointing, Giving, Showing, and Child-initiated Joint attention [duration in seconds]; and combined EScs and mother-child interaction observations - JA initiation composite, and JA responses composite) **Indirect outcomes:** **Coexisting problems or disorders: Speech and language** (as measured by the Reynell Developmental Language Scale - Receptive Language and Expressive Language subscales); and **IQ** (as measured by the Mullen Scales of Early Learning [MSEL] - Developmental quotient)
Study Design	RCT
Source of funding	NIH grant HD035470 and the CPEA network
Limitations	1. Risk of selection bias is unclear/unknown as the randomisation method is unclear and insufficient detail is reported with regards to allocation concealment 2. High risk of performance bias as intervention administrators were non-blind 3. High risk of response bias as participants were non-blind 4. Risk of selective reporting bias is unclear/unknown as the protocol is not registered on ClinicalTrials.gov
Notes	Data for symbolic play not extracted as outside scope

1.1.16 KASARI2010

Study ID	KASARI2010
Bibliographic reference	Kasari C, Gulsrud AC, Wong C, Kwon S, Locke J. Randomized controlled caregiver mediated joint engagement intervention for toddlers with autism. Journal of Autism and Developmental Disorders. 2010;40:1045-1056.
Methods	**Allocation:** Randomised **Matching:** No matching **Blindness:** Outcome assessors are blinded but intervention administrators, parents and participants are non-blind **Setting:** Not reported **Raters:** Reviewers blind to group status and time point scored **Country:** USA
Participants	**Diagnosis:** DSM-IV Autism **Coexisting conditions:** Exclusion criteria included additional syndromes **Qualifying Diagnostic Assessment:** Clinical diagnosis was corroborated using the Autism Diagnostic Interview-Revised (ADI-R) **N:** 38 **Age:** 1.8-3 years (mean: 2.6 years) **Sex:** 24% female **Ethnicity:** 58% white **IQ:** Range not reported (mean: 62.3) **Inclusion criteria:** Children were included if they: were younger than 36 months and met DSM-IV criteria for autism (diagnosed by an independent clinician) **Exclusion criteria:** Children were excluded if they had any additional syndrome
Interventions	**Experimental Intervention: Joint attention training** adapted from Kasari et al.(2006, 2008). Like that previous intervention, this intervention involved techniques such as following the child's lead and interest in activities, talking about what the child was doing, repeating back and expanding child utterances, giving corrective feedback, sitting close to and making eye-contact with the child, and making environmental adjustments to engage the child. However, for this intervention the joint attention training was caregiver-mediated and caregivers as well as children received 30 minutes of direct instruction and handouts that summarized the main objectives of each module **Delivery of intervention:** Graduate students in educational psychology **Format or method of administration:** Parent-child dyad **Intensity:** 12 hours (3 x 0.5hour/week) **Duration of intervention:** 8 weeks **Total duration of follow-up:** 52 weeks (assessments were also performed at 52 weeks for the experimental group but as there was no control at this time point data is not extracted)
Outcomes	**Direct outcome:** **Core autism feature: Impaired reciprocal social communication and interaction** (as measured by behaviour observations of mother-child coded for joint engagement, frequency of joint attention initiations, and frequency of joint attention responses)
Study Design	RCT
Source of funding	NIMH grant MH064927 awarded to Connie Kasari

Limitations	1. Risk of selection bias is unclear/unknown as there is insufficient detail reported with regards to allocation concealment 2. High risk of performance bias as intervention administrators are non-blind 3. High risk of response bias as participants and parents are non-blind
Notes	This trial is registered on ClinicalTrials.gov, study NCT00065910

1.1.17KASARI2012

Study ID	KASARI2012
Bibliographic reference	Kasari C, Rotherham-Fuller E, Locke J, Gulsrud A. Making the connection: randomized controlled trial of social skills at school for children with autism spectrum disorders. Journal of Child Psychology and Psychiatry. 2012;53:431-439.
Methods	**Allocation:** Randomised (block randomised by class) **Matching:** Stratified randomisation by school grade **Blindness:** Participants and intervention administrators were non-blind. Blinding of typically developing peer and teacher outcome assessments is unclear. There was, however, an independent and blinded behavioural observation measure **Setting:** Educational (school) **Raters:** Self-completed, typically-developing peer-completed, teacher-completed and a behavioural observation measure rated by independent and blinded observers **Country:** USA
Participants	**Diagnosis:** ASD **Coexisting conditions:** None reported **Qualifying Diagnostic Assessment:** Autism Diagnostic Interview-Revised (ADI-R) and Autism Diagnostic Observation Schedule (ADOS) administered by blind and independent psychologists **N:** 60 **Age:** Range not reported but inclusion criteria 6-11 years (mean: 8.1 years) **Sex:** 10% female **Ethnicity:** 47% white **IQ:** Range not reported but inclusion criteria >=65 (mean: 90.97) **Inclusion criteria:** Participants were included if they: met criteria for ASD on the ADI-R and ADOS; were fully included in a regular education classroom for at least 80% of the school day and were in grades 1-5; were aged 6-11 years old; had an IQ >=65 **Exclusion criteria:** Participants were excluded if they had additional diagnoses
Interventions	**Experimental Intervention: Four-armed trial, including waitlist control and:** **Individual social-communication intervention (CHILD):** Children with ASD were taught social communication skills based on individualized skill deficits and using techniques including adult coaching, modeling, reinforcement and feedback. Participants were set homework assignments to practice strategies and skills in social interactions to encourage generalization **Peer-mediated social skills group (PEER):** Three typically-developing children from the target autistic child's classroom attended a social skills group and were taught strategies for engaging with children with social challenges in the playground. Techniques for teaching the typically-developing peers included social modeling and reinforcement, and homework assignments were set to encourage practice. **Both individual and peer-mediated social-communication intervention:** See above **Delivery of intervention:** Intervention was delivered by seven graduate students in educational psychology. Group size for PEER condition not reported. **Format or method of administration:** Individual for CHILD condition and

	group-based for PEER **Intensity:** Actual intensity not reported but planned intensity of 4 hours (0.67 hour/week) **Duration of intervention:** 6 weeks **Total duration of follow-up:** 12 weeks (includes 6-week post-intervention follow-up)
Outcomes	**Direct outcome:** **Core autism feature: Impaired reciprocal social communication and interaction** (as measured by the Social Network Survey [SNS] - Social Network Salience Ratio, Number of received friendship nominations [Indegrees] and Rejections; Teacher Perception of Social Skills [TPSS]; and Playground observation of peer engagement - percentage of intervals the child spent jointly engaged with others)
Study Design	RCT
Source of funding	NIMH 5-U54-MH-068172 and HRSA UA3MC11055
Limitations	1. Unclear/unknown risk of selection bias due to statistically significant baseline differences (83% of the female participants were randomised to the peer-mediated condition). The randomisation method was also unclear and there was insufficient detail reported with regards to allocation concealment 2. High risk of performance bias as intervention administrators were non-blind to group assignment 3. High risk of response bias as participants were non-blind to group assignment 4. Risk of detection bias is unclear/unknown for most outcome measures (with the exception of behavioural observations) as there was no independent reliability or validity data and the blinding of outcome assessors was unclear.
Notes	This trial is registered on ClinicalTrials.gov, Study NCT00095420. Data could not be extracted from the paper due to the reporting in a 2x2 matrix, however, disaggregated data (split out into the 4 arms) was requested and supplied by authors. For the outcome overview meta-analysis, only the blinded behavioural observation outcome measure of joint engagement for the peer-mediated condition is extracted as this was the only outcome measure which was analogous to those reported for other studies and the peer-mediated condition was found to be more effective than the individual intervention condition examined.

1.1.18 KOENIG2010

Study ID	KOENIG2010
Bibliographic reference	Koenig K, Williams White S, Pachler M, Lau M, Lewis M, Klin A, et al. Promoting social skill development in children with pervasive developmental disorders: a feasibility and efficacy study. Journal of Autism and Developmental Disorders. 2010;40:1209-1218.
Methods	**Allocation:** Randomised **Matching:** No matching **Blindness:** Blinded raters for one outcome measure but that measure relied on parent report and parents, participants and intervention administrators were non-blind **Setting:** Not reported **Raters:** Parent-report or parent-completed **Country:** USA
Participants	**Diagnosis:** ASD (24% autism, 21% Asperger's disorder, and 55% PDD-NOS) **Coexisting conditions:** None reported **Qualifying Diagnostic Assessment:** Clinical diagnosis of pervasive developmental disorder was corroborated using the Autism Diagnostic Observation Schedule (ADOS), the Social Communication Questionnaire (SCQ) and the Pervasive Developmental Disorders Behavior Inventory **N:** 44 **Age:** Range not reported but inclusion criteria 8-11 years (mean: 9.2 years) **Sex:** 23% female **Ethnicity:** 98% white **IQ:** Range not reported but inclusion criteria FIQ>70 (mean: 96.2) **Inclusion criteria:** Children were included if they: were aged 8-11 years; had a FIQ>=70; and had a clinical diagnosis of pervasive developmental disorder and met criteria for a pervasive developmental disorder on the ADOS, the SCQ and the Pervasive Developmental Disorders Behavior Inventory **Exclusion criteria:** Children were excluded if they had psychiatric problems requiring an alternative treatment, in particular, severe aggression, self-injury or oppositional behaviour as defined by a score >=18 on the irritability subscale of the Aberrant Behavior Checklist (ABC) or scoring in the clinically significant range on any scale of the Children's Symptom Inventory (CSI)
Interventions	**Experimental Intervention: Social skills groups** consisting of 4-5 autistic participants and 2 typically-developing peer tutors. Techniques were based on social learning theory and principles of behaviour theory. Each group session involved two activities that required group members to socialize with peers, including playing cooperatively, taking turns, listening to one another, solving a problem or tolerating frustration and change. **Delivery of intervention:** Intervention delivered in groups of 6-7 (with 4-5 participants and 2 peer tutors) by two licensed clinicians (included an advance practice registered nurse, two social workers, and four clinical psychologists) **Format or method of administration:** Group **Intensity:** Actual intensity based on attendance not reported but planned intensity of 20 hours (1.25 hours/week) **Duration of intervention:** 16 weeks **Total duration of follow-up:** 16 weeks
Outcomes	**Direct outcome:**

	Core autism feature: Impaired reciprocal social communication and interaction (as measured by a dichotomous measure of positive treatment response - 'much improved/very improved' on CGI-improvement; and the Social Competence Inventory [SCI] - Pro-social index and Social initiation index)
Study Design	RCT
Source of funding	Organization for Autism Research; Beatrice Renfield- Yale School of Nursing Clinical Initiatives Fund; Research Units on Pediatric Psychopharmacology, National Institute of Mental Health
Limitations	1. High risk of performance bias as the intervention administrators were non-blind and the groups were not comparable in the care they received apart from the intervention as there was a statistically significant difference in the number of participants in each group receiving psychotropic medication (including antipsychotics, SSRIs and stimulants) with N=6 (24%) in the treatment group and N=10 (53%) in the waitlist control group 2. High risk of response bias as participants were non-blind 3. High risk of detection bias as although there was a blinded rater for the CGI the measure was based on non-blind parental report and insufficient detail is reported with regards to the other outcome measure (Social Competence Inventory [SCI]) which was also completed by non-blind parents
Notes	Not applicable

1.1.19 LANDA2011

Study ID	LANDA2011
Bibliographic reference	Landa RJ, Holman KC, O'Neill AH, Stuart EA. Intervention targeting development of socially synchronous engagement in toddlers with autism spectrum disorder: a randomized controlled trial. Journal of Child Psychology and Psychiatry. 2011;52:13-21.
Methods	**Allocation:** Randomised **Matching:** Matched on receptive language and visual reception scores on the Mullen Scales of Early Learning (MSEL) and the Autism Diagnostic Observation Schedule (ADOS) Social Interaction algorithm **Blindness:** Outcome assessors were blind to group assignment and were unfamiliar with the child. However, intervention administrators, parents and participants were non-blind **Setting:** Educational (Kennedy Krieger classroom) **Raters:** Clinician-rated **Country:** USA
Participants	**Diagnosis:** ASD **Coexisting conditions:** None reported **Qualifying Diagnostic Assessment:** Clinical diagnosis of ASD was corroborated by the ADOS **N:** 50 (but demographic data reported for available cases N=48) **Age:** Range not reported but inclusion criteria 1.75-2.75 years (mean: 2.4 years) **Sex:** 21% female **Ethnicity:** 79% white **IQ:** Range not reported (mean MSEL visual reception [VR] T-score: 29.3) **Inclusion criteria:** Children were included if they: were aged 1.75-2.75 years; had a clinical diagnosis of ASD and met criteria for an ASD on the ADOS; and had a non-verbal mental age >=8 months (as measured by the MSEL VR scale) **Exclusion criteria:** Children were excluded if: they had a sibling with ASD; English was not the primary language spoken at home; there was a known etiology for ASD
Interventions	**Experimental Intervention: Combined joint attention training and Early Behavioural Intervention (EBI).** Participants in both the control group and the experimental group received behavioural intervention using the Assessment, Evaluation, and Programming System for Infants and Children (AEPS; Bricker, 2002) curriculum. This intervention involved techniques such as discrete trial teaching and pivotal response training and alternative and augmentative communication techniques (including visual cues and schedules) to target child-initiated intentional communication and diverse object play. The intervention administrator followed the child's lead and expanded language and play behaviour. Both control and experimental interventions also included parent education classes (38 hours) focusing on behavioural strategies for enhancing child development and for behaviour management, and coping and advocacy, and home-based parent training (9 hours) focusing on techniques for improving communication and adaptive behaviour. Both experimental and control interventions included goals for joint attention and imitation. However, the experimental group differed from the control group in the number of orchestrated opportunities to respond to and initiate joint attention and imitate others during social interaction and the number of opportunities afforded by the physical environment for initiating and responding to joint

	attention and for sharing positive affect, and there was a more discrete breakdown of social targets for the experimental curriculum. **Delivery of intervention:** Intervention was delivered in a classroom, group size not reported but participant to intervention administrator ratio was 5:3. Paper does not report who administered the intervention. **Format or method of administration:** Group **Intensity:** Range not reported but intended classroom intervention intensity of 10 hours/week (means: 205.7 hours for experimental group and 196.2 hours for the control group) **Duration of intervention:** 26 weeks **Total duration of follow-up:** 52 weeks (includes 6-month post-intervention follow-up)
Outcomes	**Direct outcome:** **Core autism feature: Impaired reciprocal social communication and interaction** (as measured by the Communication and Symbolic Behavior Scales Developmental Profile [CSBS DP] - Socially engaged imitation [SEI] as defined by proportion of imitations paired with eye contact with the examiner, Initiation of joint attention [IJA], and Shared positive affect [SPA]) **Indirect outcome:** **Coexisting problem or disorder: Speech and language** (as measured by the Mullen Scales of Early Learning [MSEL] - Expressive Language and Receptive Language T-scores)
Study Design	RCT
Source of funding	National Institute of Mental Health (154-MH066417; Studies to Advance Autism Research and Treatment) and HRSA (R40 MC 15594)
Limitations	1. Risk of selection bias is unclear/unknown as the randomisation method is unclear and insufficient detail reported with regards to allocation concealment 2. High risk of performance bias as the intervention administrators and parents were non-blind 3. High risk of response bias as the participants were non-blind
Notes	This trial is registered on ClinicalTrials.gov, study NCT00106210. Contacted author regarding missing outcome data (receptive language scores) and requested data was supplied

1.1.20 LAUGESON2009

Study ID	LAUGESON2009
Bibliographic reference	Laugeson EA, Frankel F, Mogil C, Dillon AR. Parent-assisted social skills training to improve friendships in teens with autism spectrum disorders. Journal of Autism and Developmental Disorders. 2009;39:596-606.
Methods	**Allocation:** Randomised **Matching:** No matching **Blindness:** Non-blind **Setting:** Outpatient **Raters:** Self- and Parent-rated **Country:** USA
Participants	**Diagnosis:** ASD (70% high-functioning autism, 27% Asperger's disorder, and 3% PDD-NOS) **Coexisting conditions:** None reporting **Qualifying Diagnostic Assessment:** Inclusion based on previous clinical diagnosis. No corroborating diagnostic assessment for this study. **N:** 36 (but N=3 dropped out and demographic and data analysis reported for N=33) **Age:** 13-17 years (mean: 14.6 years) **Sex:** 15% female **Ethnicity:** 42% white **IQ:** Range not reported but inclusion criteria VIQ>=70 (mean VIQ: 92.3 based on Kaufman Brief Intelligence Test - Second Edition [KBIT-2]) **Inclusion criteria:** Children were included if they: were aged 13-17 years; had social problems (as reported by their parent); had a previous diagnosis of high-functioning autism, Asperger's disorder or PDD-NOS; themselves and a parent or family member were fluent English-speakers; had a verbal IQ >=70 (as measured by the KBIT-2); Verbally expressed an interest in participating in the intervention during the eligibility screening **Exclusion criteria:** Children were excluded if they had a history of major mental illness (such as bipolar disorder, schizophrenia, or psychosis) or had a hearing, visual, or physical impairment that restricted outdoor sports activities
Interventions	**Experimental Intervention: Program for the Education and Enrichment of Relational Skills (PEERS) social skills group.** This intervention was based on an adapted teen-appropriate version of the program developed by Frankel and Myatt (2003). Concurrent parent and teen sessions addressed: reciprocal conversational skills (and how parents could identify activities which might lead to potential friendships); appropriate use of electronic communication in developing pre-existing friendships (and parents taught the social structure of school peer groups); how to choose appropriate friends by pursuing extra-curricular activities and identifying groups they might fit in with; how to join (and exit) conversations with peers; how to organise and host a get-together with friends; how to be a good sportsman during games and sports; strategies for handling teasing and bullying appropriately and for changing a bad reputation; and strategies for handling disagreements with peers. Each session involved didactic instruction, role-play by the intervention administrators of the appropriate social skill, rehearsal of the social skill by the teen with accompanying performance feedback, and a homework assignment for the next session (parents were instructed on how to overcome obstacles associated with their child completing the upcoming homework assignment).

	Delivery of intervention: Intervention was delivered by clinical psychologists to groups of approximately seven participants **Format or method of administration:** Group **Intensity:** Actual intensity accounting for group attendance not reported but planned intensity was 18 hours (1.5 hours/week) **Duration of intervention:** 12 weeks **Total duration of follow-up:** 24 weeks (12 week intervention and waitlist control period followed by 12 weeks active intervention for the waitlist control)
Outcomes	**Direct outcome:** **Core autism feature: Impaired reciprocal social communication and interaction** (as measured by a study-specific questionnaire - the Test of Adolescent Social Skills Knowledge [TASSK]; the Friendship Qualities Scale [FQS]; and the Social Skills Rating System [SSRS] - Social skills standardized score)
Study Design	RCT
Source of funding	NIH Training Grant #T32-MH17140, Andrew Leuchter, Principal Investigator. The writing of this paper was partially supported by NIMH Grant #1U54MH068172, Fred Frankel, Project Principal Investigator
Limitations	1. Risk of selection bias is unclear/unknown as randomisation method is unclear and there is insufficient detail reported with regards to allocation concealment 2. High risk of performance bias as intervention administrators were non-blind 3. High risk of response bias as participants were non-blind 4. High risk of detection bias as outcome measures based on non-blind self- and parent-report
Notes	Data could not be extracted for the blinded teacher-rated outcome measures as poor return rate meant that N<10/arm for analysis. Data were not extracted for Quality of Play Questionnaire (QPQ) - Host as given that the intervention was parent-assisted and this outcome measure relied on parental assistance in order to set up a play date it was a fidelity measure rather than a measure of clinical efficacy Contacted author regarding missing outcome data and requested data was supplied

1.1.21 LOPATA2010

Study ID	LOPATA2010
Bibliographic reference	Lopata C, Thomeer ML, Volker MA, Toomey JA, Nida RE, Lee GK, et al. RCT of a manualized social treatment for high-functioning autism spectrum disorders. Journal of Autism and Developmental Disorders. 2010;40:1297-1310.
Methods	**Allocation:** Randomised **Matching:** Stratified randomisation based on age, gender and ethnicity **Blindness:** Non-blind **Setting:** College campus **Raters:** Parent- and researcher-rated **Country:** USA
Participants	**Diagnosis:** ASD (78% Asperger's Disorder) **Coexisting conditions:** None reported **Qualifying Diagnostic Assessment:** Participants were required to have a written diagnosis of ASD and two senior researchers independently reviewed parent-provided documentation and relevant evaluations and records using a standardized checklist to agree if information supported an ASD. **N:** 36 **Age:** Range not reported but groupings by age are 7-12 years (mean: 9.5 years) **Sex:** 6% female **Ethnicity:** 89% white **IQ:** Range not reported but inclusion criteria FIQ>70 (mean: 103; as measured by the Wechsler Intelligence Test for Children - 4th ed. [WISC-IV] Short form) **Inclusion criteria:** Children were included if they had: a written diagnosis of ASD; a full-scale IQ>70 (as measured by the WISC-IV-Short form); a score >=80 on the WISC-IV Verbal Comprehension Index or Perceptual Reasoning Index; a score >=80 on a short form of the Comprehensive Assessment of Spoken Language. **Exclusion criteria:** Children were excluded for severe physical aggression
Interventions	**Experimental Intervention: Social skills groups.** Intervention was delivered in groups (by age) and targeted skills were social skills, emotion recognition and interpretation of non-literal language. Intervention was manualized (Lopata et al., 2008) and techniques included direct instruction, modelling, role play, performance feedback, team-working to complete task or solve problem, a response-cost reinforcement system, and homework assignments. Intervention also involved weekly concurrent parent training sessions which focused on increasing understanding of autism and of the intervention that their child was taking part in, and on teaching parents strategies to encourage generalization. **Delivery of intervention:** Intervention delivered by graduate and undergraduate students from fields of psychology or education (N=3 per group) to groups of 6 children who were grouped by age (7-8 year olds, 9-10 year olds, and 11-12 year olds) **Format or method of administration:** Group **Intensity:** Actual intensity not reported was planned intensity was 204 hours (41 hours/week, consisting of 5 1.2 hour-sessions a day every day for 5 weeks) **Duration of intervention:** 5 weeks **Total duration of follow-up:** 6 weeks (post-intervention assessments completed during the 5 days following treatment)

Outcomes	**Direct outcome:** **Core autism feature: Impaired reciprocal social communication and interaction** (as measured by a study-specific questionnaires - the Adapted Skillstreaming Checklist [ASC] designed as a direct measure of skills taught and Skillstreaming Knowledge Assessment [SKA]; Social Responsiveness Scale [SRS] - Total; Behavior Assessment System for Children, 2nd ed., parent rated [BASC-2-PRS] - Social skills; and Diagnostic Analysis of Nonverbal Accuracy 2 [DANVA2] - Child faces that is a measure of emotion recognition) **Coexisting problem or disorder: Speech and language** (as measured by the Comprehensive Assessment of Spoken Language [CASL] - Idiomatic Language) **Indirect outcomes:** **Behaviour that challenges** (as measured by the BASC-2-PRS - Withdrawal)
Study Design	RCT
Source of funding	Not reported
Limitations	1. Risk of selection bias is unclear/unknown as insufficient detail reported with regards to allocation concealment 2. High risk of performance bias as intervention administrators were non-blind 3. High risk of response bias as participants were non-blind 4. High risk of detection bias as parent- and researcher-rated outcome measures were non-blind 5. High risk of selective reporting bias as there were no staff-rated outcome measures for the waitlist control group and data cannot be extracted for parent, staff and child satisfaction surveys
Notes	

1.1.22 OWENS2008

Study ID	OWENS2008
Bibliographic reference	Owens G, Granader Y, Humphrey A, Baron-Cohen S. LEGO therapy and the social use of language programme: an evaluation of two social skills interventions for children with high functioning autism and Asperger syndrome. Journal of Autism and Developmental Disorders. 2008;38:1944-1957.
Methods	**Allocation:** Randomised **Matching:** Matched into pairs based on availability, chronological age, IQ, autism severity (as assessed by the Gilliam Autism Rating Scale [GARS]), and VIQ **Blindness:** Non-blind (participants and intervention administrators were not blind. The outcome measures were also largely non-blind in that they were assessed by the intervention administrator or relied on parental report and the blinding of parents was unclear) **Setting:** Educational (school) **Raters:** Parent-completed, parent interview (conducted by blinded research assistant) or intervention administrator **Country:** UK
Participants	**Diagnosis:** ASD (19% high-functioning autism; 52% Asperger syndrome; 19% ASD and 10% autism) **Coexisting conditions:** None reported **Qualifying Diagnostic Assessment:** Clinical diagnosis made by a clinical psychologist, psychiatrist or paediatrician was corroborated using the Autism Diagnostic Interview-Revised (ADI-R) **N**: 31(note that an additional 16 participants were excluded as they made up the no intervention control group which did not meet inclusion criteria given that it was retrospective and non-randomly assigned) **Age:** Range not reported but inclusion criteria 6-11 years (mean: 8.2 years) **Sex:** 3% female **Ethnicity:** Not reported **IQ:** Range not reported but inclusion criteria IQ>70 (mean IQ: 110.5; mean VIQ: 105.7) **Inclusion criteria:** Participants were included if they: had a current diagnosis of ASD, high-functioning autism, autism or Asperger Syndrome made by a clinical psychologist, psychiatrist or paediatrician and confirmed using the ADI-R; were aged 6-11 years old; had an IQ>70; were able to speak in phrases; were attending mainstream education or an inclusion unit within a mainstream school **Exclusion criteria:** Participants were excluded if they: were currently receiving other behavioural interventions or social skills groups; had additional diagnoses of childhood psychoatric disorders
Interventions	**Experimental Intervention: LEGO therapy:** This intervention involved collaborative LEGO play in pairs or small groups (based on a draft manual produced by Dr. LeGoff). Typical projects included building a LEGO set in groups of three with each member of the group assigned a different role (for instance, "engineer", "supplier" and "builder") and "freestyle" LEGO activities in which children designed and built a model in pairs (for instance, a space rocket). The former project type aimed to target joint attention, turn taking, sharing, joint problem solving, listening and general social communication

	skills. While, the "freestyle" projects aimed to target compromise, clear expression of ideas and taking other people's perspectives and ideas into account. During the intervention children were asked to follow "LEGO Club Rules", which included: "Build things together"; "If someone else is using it, don't take it, ask first"; "Use indoor voices-no yelling"; and "Use polite words". The therapists role was to highlight the presence of a problem and help children to come up with their own solutions (or remind them of strategies which they had previously used) rather than pointing out specific social problems or solutions. In each session, several social issues would arise and the therapist would intervene approximately every 5 minutes. Children were awarded on the basis of individual skill achievement in the form of a certificate presented in front of the group. There were three levels of skill attainment with the highest level, "LEGO Creators", describing children who were able to build models in groups and design freestyle models in pairs without adult help. **Control Intervention: Social Use of Language Programme (SULP; Rinaldi, 2004):** This intervention used a direct group-based teaching approach (following the SULP manual) to target eye contact, listening, turn taking, proxemics and prosody. Instruction followed a specified framework, beginning with stories about monster characters who experienced problems with particular social or communication skills, moved on to asking the children to evaluate adult models of good and bad skills, and finally children practised the targeted skill through games and conversation. Children were rewarded for sitting and listening appropriately with a sticker chart (leading to sweets) **Delivery of intervention:** Group sizes ranged from 3 to 6 and the both experimental and control interventions were delivered by the first author investigator (a graduate student) **Format or method of administration:** Group-based **Intensity:** Actual intensity was not reported but planned intensity was 18 hours (1 hour/week) **Duration of intervention:** 18 weeks **Total duration of follow-up:** 18 weeks
Outcomes	**Direct outcome:** **Core autism feature: Impaired reciprocal social communication and interaction** (as measured by the Gilliam Autism Rating Scale [GARS] - Social Interaction subscale; and behavioural observations in the playground of frequency of child-initiated social interactions with familiar TD peers, and duration of all social interactions with familiar TD peers) **Indirect outcomes:** **Coexisting problem or disorder: Adaptive behaviour** (as measured by the Vineland Adaptive Behavior Scales [VABS] - Socialization and Communication subscales) **Behaviour that challenges** (as measured by the VABS - Maladaptive Behavior Index)
Study Design	RCT
Source of funding	Studentship from Medical Research Council
Limitations	1. Risk of selection bias is unclear/unknown as the randomisation method is unclear and insufficient detail is reported with regards to allocation concealment 2. High risk of performance bias as intervention administrator was not blinded

	3. High risk of response bias as participants were not blinded 4. Risk of detection bias was different for different outcome measures with unclear/unnown risk of detection bias for GARS as parent-completed and unclear if blinded to group assignment and for VABS as although the interviewer was a blinded research assistant, the outcome measure was based on non-blind parent report and high risk of detection bias for behavioural observations as outcome assessor was non-blind investigator 5. Risk of selective reporting bias is unclear/unknown as the trial is not registered on ClinicalTrials.gov 6. High risk of other bias due to potential conflict of interest as LEGO materials were provided free of charge
Notes	Data was not extracted for the no intervention control group (N=16) as this was retrospective and non-randomly assigned. Author was contacted as no sample sizes for analysis reported in the evidence tables and requested information was supplied.

1.1.23 ROEYERS1996

Study ID	ROEYERS1996
Bibliographic reference	Roeyers H. The influence of nonhandicapped peers on the social interactions of children with a pervasive development disorder. Journal of Autism and Developmental Disorders. 1996;26:303-320.
Methods	**Allocation:** Randomised **Matching:** Matched on chronological age and sex **Blindness:** Outcome assessors were blind, however, intervention administrators and participants were non-blind **Setting:** Educational (school) **Raters:** Five well-trained observers not familiar with the purposes of the project. All observations were double-coded. **Country:** Belgium
Participants	**Diagnosis:** DSM-III-R ASD (87% Autistic disorder and 13% PDD-NOS) **Coexisting conditions:** None reported **Qualifying Diagnostic Assessment:** None reported and unclear who assessed whether children met DSM-III-R criteria **N:** 85 **Age:** 5-13 years (mean: 9.3 years) **Sex:** 32% female **Ethnicity:** Not reported **IQ:** Continuous measure of IQ not reported (Categorical data: 24% IQ>69; 26% IQ 50-69; 51% IQ<50) **Inclusion criteria:** Not reported **Exclusion criteria:** Not reported
Interventions	**Experimental Intervention: Play sessions with typically developing peers.** Typically developing peers attended a 1.25 hour preparatory session consisting of education about autism and role-playing activities that addressed how to react to aggressive behaviour, how to remain on the same level as the child with autism, i.e. sitting or standing, and alternative ways to get the attention of the child with autism when verbal attempts have failed. Intervention sessions consisted of 30 minute free-play sessions between a child with autism and a typically developing child in a playroom familiar to the child with autism once or twice a week during lunchtime or after school. Generalization of skills was tested by conducting one free-play session with an unfamiliar typically developing peer and one free-play session with a peer with autism **Delivery of intervention:** Intervention was delivered by a typically-developing peer **Format or method of administration:** TD-ASD child dyad **Intensity:** Actual intensity accounting for session attendance was not reported, however, planned intensity was 7.5 hours (0.5-1 hour/week) **Duration of intervention:** 15 sessions (children had 1-2 sessions a week) **Total duration of follow-up:** 15 sessions (children had 1-2 sessions a week)
Outcomes	**Direct outcome:** **Core autism feature: Impaired reciprocal social communication and interaction** (as measured by behavioural observations with a familiar typically-developing peer [coded for frequency of social interactions and child-initiated social interaction]

Study Design	RCT
Source of funding	Belgian National Fund for Scientific Research
Limitations	1. Risk of selection bias is unclear/unknown as the randomisation method is unclear and insufficient detail is reported with regards to allocation concealment 2. High risk of performance bias as intervention administrators were non-blind 3. High risk of response bias as participants were non-blind 4. High risk of selective reporting bias as data could not be extracted for the Social Behavior Rating Scale
Notes	Not all behavioural observation outcome measures were extracted, instead outcome measures extraction was restricted to those considered most clinically relevant.

1.1.24 RUBLE2010

Study ID	RUBLE2010
Bibliographic reference	Ruble LA, Dalrymple NJ, McGrew JH. The effects of consultation on individualized education program outcomes for young children with autism: the collaborative model for promoting competence and success. Journal of Early Intervention. 2010;32:286-301.
Methods	**Allocation:** Randomised **Matching:** Where more than one teacher was participating per school stratified randomisation was used with participating teachers randomised in pairs within schools **Blindness:** Teachers and intervention administrators were non-blind and blinding of child participants is unclear. The primary outcome assessor was also non-blind with a blinded secondary outcome assessor only rating 20% of behavioural observations **Setting:** Educational (primary placement for educational services was as follows: 43% special education, 23% general education, 23% inclusive preschool, 11% segregated preschool) **Raters:** Investigator-rated **Country:** USA
Participants	**Diagnosis:** DSM-IV-TR Autistic disorder **Coexisting conditions:** None reported **Qualifying Diagnostic Assessment:** Participants were screened using the Modified Checklist for Autism in Toddlers (MCHAT, for children aged<4 years) or the Social Communication Questionnaire (SCQ, for children aged >4 years) and diagnosis was corroborated using the Autism Diagnostic Interview-Revised and the Autism Diagnostic Observation Schedule-Generic (ADOS-G) **N:** 35 **Age:** 3-8 years (mean: 6.1 years) **Sex:** 17% female **Ethnicity:** 74% white **IQ:** Range not reported (mean: 46.8 as assessed using the Differential Abilities Scales) **Inclusion criteria:** Children were included if they: received special education services and were designated by the Individuals with Disabilities Education Act under the category of autism; scored above cut-off on the Modified Checklist for Autism in Toddlers (MCHAT, for children aged<4 years) or the Social Communication Questionnaire (SCQ, for children aged >4 years); met DSM-IV-TR criteria of autistic disorder corroborated using the ADI-R and ADOS-G **Exclusion criteria:** Not reported
Interventions	**Experimental Intervention: Teacher consultation and training according to the collaborative model for promoting competence and success (COMPASS).** The aims of COMPASS are to promote collaboration between school personnel and carers when initially generating interventions, link assessment information and program plan development, prevent behaviour that challenges by placing emphasis on acquisition of functional skills and accompanying environmental supports and develop teaching strategies only after objectives are identified. In the current study three goal areas were targeted as being critical for children with autism: social skills, communication

	and independence. During an initial consultation (2.5-3 hour meeting) investigators met with teachers and parents (within the first 1.5 months of the start of the school year) and the general background for the COMPASS consultation was explained, teachers' and parents' concerns were identified, the three targeted area goals were identified and prioritised and concerns were then translated into specific Individualised Education Program (IEP) objectives, following development of objectives in the three targeted skills areas investigators worked with teachers to develop teaching plans for those objectives. After the initial consultations, teachers had four 1.5-hour coaching visits (approximately every 6 weeks) where teacher-child dyads were observed and videotaped focusing on the three targeted objectives, children's levels of progress were coded using Goal Attainment Scaling (GAS) and teachers were interviewed. During the coaching visits investigators provided feedback to teachers, and where necessary modelled instructional behaviours or helped teachers adapt materials and activities. After each coaching visit teachers and parents were provided with summary reports including descriptions of observations, information from teacher interviews, progress reports using GAS forms, and recommendations to be followed before the next coaching visit. **Delivery of intervention:** Intervention delivered by investigators (first and second authors) **Format or method of administration:** Teacher-child dyads **Intensity:** Actual intensity not reported but planned intensity was 9 hours over the school year (one initial 2.5-3 hour consultation and four 1.5-hour coaching sessions approximately 6 weeks apart) **Duration of intervention:** 39 weeks (one school year) **Total duration of follow-up:** 39 weeks (one school year)
Outcomes	**Direct outcome:** **Core autism feature: Overall autistic behaviours** (as measured by behavioural observation of IEP goal attainment for targeted objectives which were social skills, communication and independence)
Study Design	RCT
Source of funding	National Institute of Mental Health (Grant No. R34MH073071)
Limitations	1. Risk of selection bias is unclear/unknown as randomisation method is unclear and insufficient detail reported with regards to allocation concealment 2. High risk of performance bias as intervention administrators non-blind 3. Risk of response bias is unclear/unknown as paper states 'single-blind' but gives no further detail with regards to whether it is the participants who are blinded 4. High risk of detection bias as primary outcome assessor was the non-blind investigator with a blinded secondary outcome assessor only rating 20% of behavioural observations. In addition, because only 20% of observations were double-coded and a standardized observation measure was not used the reliability and validity of this outcome measure is unclear 5. Risk of selective reporting bias is unclear/unknown as the trial protocol is not registered on ClinicalTrials.gov or ISRCTN
Notes	Not applicable

1.1.25 RYAN2010

Study ID	RYAN2010
Bibliographic reference	Ryan C, Charragain CN. Teaching emotion recognition skills to children with autism. Journal of Autism and Developmental Disorders. 2010;40:1505-1511.
Methods	**Allocation:** Randomised **Matching:** No matching **Blindness:** Participants, parents and outcome assessors were not blind to group allocation. Blinding of outcome assessors is unclear. **Setting:** Not reported **Raters:** The outcome assessor was an independent psychologist **Country:** Ireland
Participants	**Diagnosis:** ICD-10 diagnosis of Childhood Autism **Coexisting conditions:** Not reported **Qualifying Diagnostic Assessment:** ADOS (Autism Diagnostic Observation Schedule) & DISCO (Diagnostic Interview for Social and Communication Disorders) **N:** 33 **Age:** Range: 6.72-14.25 years (Mean: 9.5 years) **Sex:** 9% female **Ethnicity:** Not reported **IQ:** Full scale IQ not reported. Verbal and non-verbal IQ scores were available for N=25 (group allocation not reported). Mean verbal IQ on the Peabody Picture Vocabulary Test-Revised (PPVT:R) was 85.6 for the treatment group and 90.22 for the control group. Mean non-verbal IQ on the Raven Standard Progressive Matrices (SPM) 104.6 for the treatment group and 98.6 for the control group **Inclusion criteria:** Children were included if they had been referred to North Lee ASD services and had had an ICD-10 diagnosis of childhood autism confirmed through multidisciplinary assessments undertaken by the Regional Autism Service (including the autism diagnostic observation schedule [ADOS] and the diagnostic interview for social communication disorders [DISCO]) **Exclusion criteria:** Children were excluded if they had difficulty understanding the six emotion labels (happy, sad, angry, surprised, disgusted, afraid) or scored above 80% in the Emotion Recognition Test.
Interventions	**Experimental Intervention: Emotion Recognition Training.** Children were taught emotion recognition skills using exemplars and highlighting component parts of the six core emotions (happy, sad, angry, scared, surprised and disgusted). Teaching techniques included role play using emotional expressions, tracing and drawing facial expressions, face-emotion matching and homework assignments. Parents were encouraged to help children with their homework assignments and were invited to attend an information session about the teaching methods being used with their children **Delivery of intervention:** The intervention was delivered to groups of 4-7 children. The intervention was delivered by two therapists **Format or method of administration:** Group **Intensity:** Children were required to attend weekly, hour-long sessions. A total of 4 hours **Duration of intervention:** 4 weeks **Total duration of follow-up:** 18 weeks (including 3 month follow-up but no

	control group data for follow-up)
Outcomes	**Direct Outcome** **Core autism feature: Impaired reciprocal social communication and interaction, relating to emotion recognition** (as measured by the Ekman emotion recognition photographs)
Study Design	RCT
Source of funding	COPE Foundation
Limitations	1. Unclear risk of selection bias: Method of randomisation and concealment of allocation not reported 2. High risk of performance bias: Care confounds for the control group have not been reported. Participants and individuals responsible for administering care were not blind to treatment allocation 3. Unclear risk of detection bias: No information on the validity or reliability of the measure was reported and it is unclear if the outcome assessor was blinded to the treatment allocation. 4. Unclear risk of attrition bias: N=5 participants dropped out from the study prior to follow-up, but the group allocation of these participants is not reported 5. Unclear risk of selective reporting: All outcomes were reported but the study was not registered
Notes	The published paper provided limited information in the results section. A request was sent to the authors for further information, so results reported are from unpublished data.

1.1.26 SCHERTZ2013

Study ID	SCHERTZ2013
Bibliographic reference	Schertz HH, Odom SL, Baggett KM, Sideris JH. Effects of joint attention medication learning for toddlers with autism spectrum disorders: an initial randomised controlled study. Early Childhood Research Quarterly. 2013;28:249-258.
Methods	**Allocation:** Randomised **Matching:** Randomised in pairs based on order qualified for participation **Blindness:** Outcome assessors of behavioural observations were research assistants who were blind to treatment allocation. Outcomes assessors for standardised assessments were research assistants who were not blind to treatment allocation. **Setting:** Home-based **Raters:** All outcomes were rated by research assistants **Country:** USA
Participants	**Diagnosis:** Autism Spectrum Disorder (diagnostic classification not reported) **Coexisting conditions:** Details of coexisting conditions not reported **Qualifying Diagnostic Assessment:** Autism Diagnostic Observation Schedule (ADOS) and Modified Checklist for Autism in Toddlers (M-CHAT) **N:** 23 **Age:** Range: not reported (mean: 2.2 years) **Sex:** Not reported **Ethnicity:** Not reported (primarily caucasian)

	IQ: Not reported **Inclusion criteria:** Children were included if they: were less than 30 months old at recruitment; were rated as high risk for ASD based on the M-CHAT; met criteria for ASD based on the ADOS (cut-off of 4 for both the communication and social sections); did not show joint attention during behavioural observation of parent-child interaction. **Exclusion criteria:** Children were excluded if they had a diagnosis of another, potentially confounding disorder, including Down's Syndrome or birth >6 weeks premature.
Interventions	**Experimental Intervention: Joint Attention Mediated Learning (JAML) intervention.** This intervention was delivered via parent-mediation in their homes. The intervention targets progressed through three phases: the focusing on faces (FF) phase where the child was helped to look freely and often to the parent's face; the turn-taking (TT) phase where the child and parent engage in reciprocal and repetitive play that acknowledges the other's shared interest by accommodating the parent's turn; and the joint attention (JA) phase where triadic engagement is encouraged using toys. Each session began with a 10 minute interaction between the parent and child, which was recorded and then discussed, focusing on how/whether previously taught skills had been adopted and feedback and advice was offered. In between sessions, parents were required to spend 30 minutes a day with the child, integrating what had been learnt into other daily activities. Parents were given written manuals to follow, which described each unit in terms of the aim, how this could be achieved and helpful suggestions from from other parents. Parents were required to complete a daily log of interactions. The intervention was 'complete' when children showed three examples of initiating joint attention in multiple sessions. **Delivery of intervention:** Intervention was delivered by an intervention coordinator (two of whom had master's degrees in early childhood education and one had an Ed.S. degree in counselling) in the home **Format or method of administration:** Parent-child dyad **Intensity:** No details on number of hours delivered per week are reported. **Duration of intervention**: 17-52 weeks (Mean: 30 weeks) **Total duration of follow-up:** Follow-up assessments were completed 4-8 weeks after post-intervention measures were completed. The maximum time participants were followed for was 60 weeks.
Outcomes	**Direct outcome:** **Core autism feature: Impaired reciprocal social communication and interaction** (as measured by the Precursors of Joint Attention Measure [PJAM] coding of behavioural observations - Focusing on faces [FF], Turn-Taking [TT], Responding to Joint Attention [RJA] and Initiating Joint Attention [IJA]). **Indirect outcomes:** **Coexisting problems or disorders: Adaptive behaviour** (as measured by Vineland Adaptive Behaviour Scale [VABS] - Communication subscale); **Speech and language** (as measured by Mullen Scales of Early Learning [MSEL] - Receptive language, and Expressive language subscales).
Study Design	RCT
Source of funding	Grant from Autism Speaks, 1735
Limitations	1. Risk of selection bias is unclear/unknown as the method of randomisation is unclear and insufficient detail is reported with regards to allocation

	concealment 2. High risk of performance bias as intervention administrators were non-blind and potential for care confounds is not statistically tested (weekly hours of intervention [combined across sites] were 38 hours for the experimental group and 31 hours for the control group but the paper does not report any statistical testing of the significance of this difference) 3. High risk of response bias as participants were non-blind 4. Risk of detection bias was different for different outcomes: High risk for MSEL as rated by non-blind research assistants and high risk for VABS as rated by non-blind research assistants and based on interview with parents who were non-blind and involved in the intervention 5. Risk of attrition bias is unclear/unknown as no group drop-outs or incomplete data are reported 6. High risk of selective reporting bias as data is not reported for VABS subscales other than Communication
Notes	Not applicable

1.1.27 STRAIN2011

Study ID	STRAIN2011
Bibliographic reference	Strain PS, Bovey II EH. Randomized, controlled trial of the LEAP model of early intervention for young children with autism spectrum disorders. Topics in Early Childhood Special Education. 2011;31:133-154.
Methods	**Allocation:** Randomised (clustered by preschool classroom) **Matching:** Preschool classrooms matched on program dimensions such as number of program days per week (5) and length of program day (2.75-3 hours) **Blindness:** Participants and intervention administrators were non-blind. Identity and blinding of outcome assessors not reported **Setting:** Educational **Raters:** Not reported (paper only states that assessors had 5-10 years of experience with the assessment procedures, were competent, fluent in Spanish and had experience testing young children with ASD) **Country:** USA
Participants	**Diagnosis:** ASD (diagnostic classification system not reported) **Coexisting conditions:** None reported **Qualifying Diagnostic Assessment:** Not reported **N:** 56 classrooms (data analysed for 294 children) **Age:** Range not reported but all children in preschool (mean: 4.2 years) **Sex:** Not reported **Ethnicity:** Not reported **IQ:** Range not reported (mean: 61 as assessed by the Mullen Scales of Early Learning [MSEL] - Early-learning composite score) **Inclusion criteria:** Classrooms were recruited and were included if they had: children with ASD enrolled in inclsuive settings; a minimum ratio of adults to children of 1:5; a minimum ratio of typically developing peers to children with ASD of 2:1 **Exclusion criteria:** Not reported
Interventions	**Experimental Intervention: Inclusive educational intervention (Learning Experiences and Alternative Program for Preschoolers and Their Parents; LEAP) training.** The LEAP intervention is aimed at facilitating inclusion and peer-mediated intervention within the classroom. Typically developing peers are provided with comprehensive social skills training. Teachers are also trained and training includes overview of the LEAP program and of autism, classroom organisation and management, teaching strategies, teaching communication skills, providing positive behavioural guidance, monitoring progress and collecting data on IEP goals, and promoting social interactions with typically developing peers Techniques for training include written instruction and initial didactic training, observing the classroom team and providing feedback, modelling teaching and classroom procedures, involvement in planning meetings (to review/discuss new classroom and teaching strategies and activities, child progress, adaptations and modifications, successes and challenges and prioritising next steps). The LEAP intervention as implemented by teachers includes a variety of intervention approaches which are embedded in typical preschool routines (such as circle time, free play, snack and small groups) including peer-mediated interventions, errorless learning, time delay, incidental teaching, pivotal

	response training, picture exchange communication system and positive behaviour support. The LEAP intervention also includes a family skills training component involving training adult family members in behavioural teaching strategies with the aim of reducing stress and increasing pleasure in daily routines. **LEAP intervention-manual-only control.** In the control condition preschool staff were provided with intervention manuals and related written materials but not with any direct training **Delivery of intervention:** Individual administering intervention and group size not reported **Format or method of administration:** Not reported **Intensity:** 23 full days of training **Duration of intervention:** 104 weeks **Total duration of follow-up:** 104 weeks
Outcomes	**Direct outcome:** **Core autism feature: Overall autistic behaviours** (as measured by the Childhood Autism Rating Scale [CARS] - Total score) **Indirect outcomes:** **Core autism feature: Impaired reciprocal social communication and interaction** (as measured by Social Skills Rating System [SSRS] - Positive social skills [percentile rank score]) **Coexisting problems or disorders: Speech and language** (as measured by the Preschool Language Scale-4 [PLS-4] - Total score and the Mullen Scales of Early Learning [MSEL] - Receptive Language Age [months] and Expressive Language Age [months]); **IQ** (as measured by the MSEL - Early-learning composite score); **Fine and gross motor skills** (as measured by the MSEL - Fine Motor Age [months])
Study Design	RCT
Source of funding	Institute for Educational Services, US Department of Education (Grant R324E060068)
Limitations	1. Risk of selection bias is unclear/unknown as insufficient detail reported with regards to allocation concealment 2. High risk of performance bias as intervention administrators non-blind 3. High risk of response bias as participants non-blind 4. Risk of detection bias is unclear/unknown as identity and blinding of outcome assessors not reported 5. Risk of selective reporting bias is unclear/unknown as trial protocol is not registered on ClinicalTrials.gov or ISCRCTN
Notes	Not applicable

1.1.28 TANAKA2010

Study ID	TANAKA2010
Bibliographic reference	Tanaka JW, Wolf JM, Klaiman C, Koenig K, Cockburn J, Herlihy L, et al. Using computerized games to teach face recognition skills to children with autism spectrum disorder: the Let's Face It! program. Journal of Child Psychology and Psychiatry. 2010;51:944-952.
Methods	**Allocation:** Randomised **Matching:** Participants were matched on mental age and diagnosis **Blindness:** No blinding of participants, individuals responsible for administering care or outcome assessors reported **Setting:** Home-based intervention **Raters:** Not reported **Country:** USA
Participants	**Diagnosis:** DSM-IV ASD (Autism Spectrum Disorder). 56% with Autistic Disorder, 15% with Asperger's Syndrome and 29% with Pervasive Developmental Disorder not otherwise specified **Coexisting conditions:** Not reported **Qualifying Diagnostic Assessment:** ADI-R & ADOS/ADOS-G **N:** 117 (demographic and outcome data only reported for those with complete data, N=79) **Age:** Range: Not reported (Mean 10.9 years) **Sex:** 22% female **Ethnicity:** Not reported **IQ:** Range: Not reported (Mean: 94.7) As measured by the Wechsler Abbreviated Scale of Intelligence (WASI), the Wechsler Intelligence Scale for Children, 3rd edition (WISC-III), the Wechsler Adult Intelligence Scale, 3rd edition (WAIS-III), or the Differential Abilities Scales (DAS) **Inclusion criteria:** Children were included in the study if they had: a previous DSM-IV diagnosis of autism spectrum disorder corroborated using the Autism Diagnostic Observation Schedule-Generic (ADOS-G) and Autism Diagnostic Interview-Revised (ADI-R) and/or clinical consensus among two or more clinicians with at least five years experience in the field of autism; scored at least one standard deviation less than age-matched, typically developing controls on >=50% of the face processing measures, or at least 2 standard deviations less than controls on >=33% of face processing tests. **Exclusion criteria:** Children were excluded if: their vision in both eyes was worse that 20-100; based on clinical judgement, the instructions for the experimental tasks were too complicated for them to understand
Interventions	**Experimental Intervention: Let's Face It!** The 'Let's Face It!' computer program was made up of seven games that teach skills necessary for processing faces, specifically targeting areas of difficulty in children with autism including inattention to the eye area, impaired recognition of identity and failure to perceive faces holistically. The program aimed to develop skills in attending to faces generally, recognising identity and expression in faces and interpreting cues in faces. The games were accompanied by graphics and music to maintain the child's interest and the game increased in complexity as children progressed through the levels. **Delivery of intervention:** The intervention was delivered to children individually in the home environment, via a computer programme. **Format or method of administration:** Individual

	Intensity: Children were requested to play the game for at least 100 minutes per week, until they had played it for 20 hours. The mean length of intervention was 19.1 weeks. The game was played for a mean of 20.2 hours (1.06 hours per week) **Duration of intervention:** Variable. Range: Not reported (Mean: 19.1 weeks). **Total duration of follow-up:** Mean: 19.1 weeks
Outcomes	**Direct Outcome** **Core autism feature: Impaired reciprocal social communication and interaction, relating to face recognition** (as measured by the Let's Face It battery measures: Immediate Memory for Faces, Matching Identity with Masked Features, Matching Identity Across Expression, Parts/Whole Identity and Face Dimensions)
Study Design	RCT
Source of funding	NIH (studies to advance autism and treatment), James S McDonnell Foundation, National Science Foundation (#SBE-0542013) and the National Science and Engineering Research Councils of Canada.
Limitations	1. Unclear risk of selection bias: Method of randomisation and concealment of allocation method not reported 2. High risk of performance bias: No blinding of participants or individuals administering care reported 3. High risk of detection bias: No independent reliability or validity data for the Lets Face It! Skills battery and the identity and blinding of the rater is not reported for any measure 4. Unclear risk of attrition bias: Groups were not comparable for completion of intervention (experimental group N=14 lost to follow-up and control group N=7) Data missing were N=9 for intervention group and N=8 for control group 5. Unclear risk of selective reporting: The paper states that other experimental measures were taken that are not reported. Not further information about these measures reported. The study is not registered
Notes	Information regarding the subtests used for the study was not reported in this paper as it had been reported elsewhere, so was obtained from Wolf (2008). **Initial screening data** Initial screening data were missing for some participants, (ADOS: 2 missing; ADI: 5 missing). Although all the participants met the criteria for at least one of the measures, there were also participants met criteria for an autism spectrum disorder on only one and not both (ADOS: 11 did not meet; ADI: 8 did not meet). Where these situations occured, a consensus on whether to include the participant was agreed by two or more clinicians, with at least five years of experience in the field of autism spectrum disorders. These clinicians were blind to any of the outcome results for these children when making their decision. **Intensity** Participants were requested to keep playing the game until they had played for 20 hours (based on a parent-completed time-log). Due to techinical problems with the game, n=3 participants played fewer than 20 hours. The mean hours of play reported (20.2 hours) was calculated including these participants. In addition, some participants (n=not reported) discontinued game play once the intervention has started. These participants agreed to return for the follow-up measures so that their data was not lost entirely. It is

	not clear whether the mean length of play included these participants. **Unpublished data** The published paper provided limited information in the results section. A request was sent to the authors for further information, so results reported are from unpublished data.

1.1.29YOUNG2012

Study ID	YOUNG2012
Bibliographic reference	Young RL, Posselt M. Using The Transporters DVD as a learning tool for children with autism spectrum disorders (ASD). Journal of Autism and Developmental Disorders. 2012;42:984-991.
Methods	**Allocation:** Randomised **Matching:** No Matching **Blindness:** No blinding of outcome assessors reported. Participants were either assigned to an enhanced emotion recognition intervention or a standard emotion recognition group, so are likely to have been blind to treatment allocation. Parents were care administrators as this was a home-based intervention and were provided with a user-guide so were presumably non-blind to treatment allocation **Setting:** Home-based intervention **Raters:** Researchers (not further information reported) **Country:** Australia
Participants	**Diagnosis:** DSM-IV Pervasive Developmental Disorder **Coexisting conditions:** Not reported **Qualifying Diagnostic Assessment:** Participants had previously been assessed as meeting the criteria for a DSM-IV diagnosis of Pervasive Developmental Disorder by two independent practitioners and a score of >=11 on the Social Communication Questionnaire (SCQ). **N:** 25 **Age:** Not reported (Minimum: 4 years, Maximum: 8 years) **Sex:** Not reported **Ethnicity:** Not reported **IQ:** Not reported **Inclusion criteria:** Children were included if they had received a previous DSM-IV diagnosis of Pervasive Developmental Disorder (assessed by two independent practitioners) and scored >=11 on the SCQ. **Exclusion criteria:** Not reported
Interventions	**Experimental Intervention: The Transporters DVD emotion recognition training.** Children in the intervention group were given an animated 'Transporters' DVD to take and watch at home, while the control group were given an animated 'Thomas the Tank Engine' DVD. On the DVD there were 15 episodes, each lasting 5-10 minutes. The 'Transporters' DVD places a large emphasis on the emotions of the eight characters and used real human faces to support children to generalise these emotions to humans. All the scenes had plain backgrounds in the DVD so as not to distract the children from the faces of the characters. The aim of the DVD was not only to support children to recognise basic emotions (sad, happy etc), but also more complex emotions such as jealousy and feeling proud. **Control Intervention: A standard emotion recognition control DVD, ''Thomas Discovers Emotions''** was created for the present study by selecting episodes of the series that draw attention to emotions or affect. The characters in the episodes selected displayed facial expressions with depictions often being accompanied by a narration explaining the emotion. For example, ''Thomas was frightened''. There were 15 episodes on the DVD, each one lasting 5–10 minutes. A user guide was also provided with the ''Thomas Discovers Emotions'' DVD and was modelled on the guide accompanying The

	Transporter DVD. The characters in the DVD had cartoon faces and the background in Thomas the Tank Engine is exciting and detailed, encouraging attention to all areas of the screen. **Delivery of intervention:** The intervention was delivered to children in their home, through an animated DVD **Format or method of administration:** Individual **Intensity:** The planned intensity was for children to watch a minimum of three episodes a day for three weeks. The minimum total was 5.25 hours (1.75 hours per week). No information from log-files completed by parents is reported, so actual intensity information is unknown **Duration of intervention:** 3 weeks **Total duration of follow-up:** 3 weeks
Outcomes	**Direct Outcome** **Core autism feature: Impaired reciprocal social communication and interaction, relating to emotion recognition** (as measured by the Developmental Neuropsychological Assessment [NEPSY-II]: Affect Recognition subscale, The Faces Task [Baron-Cohen et al., 1997] and frequency of social behaviours from the Social Communication Questionnaire [SCQ])
Study Design	RCT
Source of funding	Not reported
Limitations	1. Risk of selection bias unclear: Method of randomisation and concealment of allocation not reported 2. Unclear risk of performance bias: Participants were blind to treatment allocation, but parents were responsible for administering care and were not blind to treatment allocation 3. High risk of detection bias: NEPSY-II and Faces Task - no independent validity and reliability information, SCQ - parent-rated and parents were intervention administrators in this study and so would be non-blind to treatment allocation or other confounding factors 4. Unclear risk of selective reporting: All outcomes are reported, but study not registered
Notes	Not applicable

1.2 CHARACTERISTICS OF EXCLUDED PSYCHOSOCIAL INTERVENTION STUDIES

1.2.1 ALDRED2012

Reason for exclusion	Efficacy data cannot be extracted

1.2.2 ALI2006

Reason for exclusion	Systematic review and no useable data could be extracted as sample sizes too small (N<10/arm)

1.2.3 ALWELL2009

Reason for exclusion	Systematic review and no useable data could be extracted as sample sizes too small (N<10/arm)

1.2.4 BELLINI2007

Reason for exclusion	Systematic review and no useable data could be extracted as sample sizes too small (N<10/arm)

1.2.5 BOYD2012

Reason for exclusion	Non-systematic review

1.2.6 CARTER2010

Reason for exclusion	Systematic review with no new useable data and any meta-analysis results not appropriate to extract

1.2.7 CHAN2009

Reason for exclusion	Systematic review with no new useable data and any meta-analysis results not appropriate to extract

1.2.8 DELANO2007

Reason for exclusion	Systematic review and no useable data could be extracted as sample sizes too small (N<10/arm)

1.2.9 DIEHL2012

Reason for exclusion	Systematic review and no useable data could be extracted as sample sizes too small (N<10/arm)

1.2.10 DISALVO2002

Reason for exclusion	Non-systematic review

1.2.11 EIKESETH2012

Reason for exclusion	Non-randomised group assignment

1.2.12 ELDEVIK2012

Reason for exclusion	Non-randomised group assignment

1.2.13 EZELL2012

Reason for exclusion	Experimental rather than clinical effectiveness study

1.2.14 FLYNN2012

Reason for exclusion	Systematic review with no new useable data and any meta-analysis results not appropriate to extract

1.2.15 GANTMAN2012

Reason for exclusion	Sample size was less than ten participants per arm (N<10/arm)

1.2.16 GERETSEGGER2012

Reason for exclusion	Trial protocol of ongoing study

1.2.17 GREENWAY2000

Reason for exclusion	Systematic review with no new useable data and any meta-analysis results not appropriate to extract

1.2.18 GULSRUD2007

Reason for exclusion	Experimental rather than clinical effectiveness study

1.2.19 HASTINGS2012

Reason for exclusion	Systematic review with no new useable data and any meta-analysis results not appropriate to extract

1.2.20 HUME2009

Reason for exclusion	Non-systematic review

1.2.21 KARKHANEH2010

Reason for exclusion	Systematic review and data could not be extracted as from dissertations and

	not reported in sufficient detail to extract

1.2.22 KASLOW2012

Reason for exclusion	Systematic review with no new useable data and any meta-analysis results not appropriate to extract

1.2.23 KIM2008

Reason for exclusion	Sample size was less than ten participants per arm (N<10/arm)

1.2.24 KOEGEL2000

Reason for exclusion	Non-systematic review

1.2.25 KOENIG2009

Reason for exclusion	Non-systematic review

1.2.26 KROEGER2007

Reason for exclusion	Non-randomised group assignment

1.2.27 KUPPENS2012

Reason for exclusion	Systematic review with no new useable data and any meta-analysis results not appropriate to extract

1.2.28 LANG2011

Reason for exclusion	Systematic review and no useable data could be extracted as sample sizes too small (N<10/arm)

1.2.29 LANOVAZ2012

Reason for exclusion	Non-systematic review

1.2.30 LAUGESON2012

Reason for exclusion	Non-randomised group assignment

1.2.31 LEGOFF2004

Reason for exclusion	Non-randomised group assignment

1.2.32 LOPATA2006

Reason for exclusion	Sample size was less than ten participants per arm (N<10/arm)

1.2.33 MAGIATI2012

Reason for exclusion	Systematic review with no new useable data and any meta-analysis results not appropriate to extract

1.2.34 MANCIL2009

Reason for exclusion	Systematic review and no useable data could be extracted as sample sizes too small (N<10/arm)

1.2.35 MCCONACHIE2005

Reason for exclusion	Non-randomised group assignment

1.2.36 MEADAN2009

Reason for exclusion	Systematic review with no new useable data and any meta-analysis results not appropriate to extract

1.2.37 NIMER2007

Reason for exclusion	Systematic review with no new useable data and any meta-analysis results not appropriate to extract

1.2.38 PATTERSON2010

Reason for exclusion	Systematic review and no useable data could be extracted as sample sizes too small (N<10/arm)

1.2.39 PAYNTER2013

Reason for exclusion	Non-randomised group assignment

1.2.40 QUIRMBACH2009

Reason for exclusion	Experimental rather than clinical effectiveness study

1.2.41 RAMDOSS2012A

Reason for exclusion	Systematic review with no new useable data and any meta-analysis results not appropriate to extract

1.2.42 RAO2008

Reason for exclusion	Systematic review with no new useable data and any meta-analysis results not appropriate to extract

1.2.43 REED2012

Reason for exclusion	Systematic review and no useable data could be extracted as sample sizes too small (N<10/arm)

1.2.44 REICHOW2010

Reason for exclusion	Systematic review with no new useable data and any meta-analysis results not appropriate to extract

1.2.45 REICHOW2012A

Reason for exclusion	Systematic review with no new useable data and any meta-analysis results not appropriate to extract

1.2.46 REICHOW2012B

Reason for exclusion	Systematic review with no new useable data and any meta-analysis results not appropriate to extract

1.2.47 REYNHOUT2006

Reason for exclusion	Systematic review with no new useable data and any meta-analysis results not appropriate to extract

1.2.48 SHUKLAMEHTA2010

Reason for exclusion	Systematic review with no new useable data and any meta-analysis results not appropriate to extract

1.2.49 SILVER2001

Reason for exclusion	Data cannot be extracted. Attempt to request data from author but email bounced back

1.2.50 SOLOMON2004

Reason for exclusion	Sample size was less than ten participants per arm (N<10/arm)

1.2.51 STRAUSS2012

Reason for exclusion	Non-randomised group assignment

1.2.52 TEST2011

Reason for exclusion	Systematic review and no useable data could be extracted as sample sizes too small (N<10/arm)

1.2.53 WANG2008

Reason for exclusion	Outcomes outside scope. Parents interactive skills were assessed pre- and post- parent training with no outcomes reported for the child and no outcomes reported regarding the impact on the family.

1.2.54WANG2009

Reason for exclusion	Systematic review with no new useable data and any meta-analysis results not appropriate to extract

1.2.55WETHERBY2006

Reason for exclusion	Non-randomised group assignment

1.2.56WHITE2011

Reason for exclusion	Systematic review with no new useable data and any meta-analysis results not appropriate to extract

1.2.57WILLIAMSWHITE2007

Reason for exclusion	Systematic review with no new useable data and any meta-analysis results not appropriate to extract

1.2.58WONG2007

Reason for exclusion	Experimental rather than clinical effectiveness study

1.3 REFERENCES OF EXCLUDED PSYCHOSOCIAL INTERVENTION STUDIES

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1.4 CHARACTERISTICS OF INCLUDED PHARMACOLOGICAL INTERVENTION STUDIES

1.4.1 HOLLANDER2005

Study ID	HOLLANDER2005
Bibliographic reference	Hollander E, Phillips A, Chaplin W, Zagursky K, Novotny S, Wasserman S, et al. A placebo controlled crossover trial of liquid fluoxetine on repetitive behaviors in childhood and adolescent autism. Neuropsychopharmacology. 2005;30:582-589.
Methods	**Allocation:** Randomised **Matching:** No matching **Blindness:** Participants, intervention administrators and outcome assessors were blinded to group assignment **Setting:** Not reported **Raters:** Clinician-rated **Country:** USA
Participants	**Diagnosis:** DSM-IV-TR autism, Asperger syndrome or PDD-NOS (87% autism and 13% Asperger syndrome) **Coexisting conditions:** None reported **Qualifying Diagnostic Assessment:** DSM-IV-TR diagnosis of ASD made by a study psychiatrist through clinician interview and the Autism Diagnostic Interview-Revised (ADI-R) and the Autism Diagnostic Observation Schedule-Generic (ADOS-G) **N:** 44 (N=44 randomised but N=39 included for demographics and data analysis) **Age:** 5-16 years (mean: 8.2 years) **Sex:** 23% female **Ethnicity:** 56% white **IQ:** 30-132 (mean: 63.7; as measured by the Wechsler Preschool and Primary Intelligence Scale-Revised [WPPSI-R, age 5-7], Wechsler Intelligence Scale for Children [WISC-III, age 7-16], the Wechsler Adult Intelligence Scale-Third Edition [WAIS-III, age 17], or the Leiter International Performance Scale-Revised [nonverbal]) **Inclusion criteria:** Children were included if they: were aged 5-17 years old; had a DSM-IV-TR diagnosis of autistic disorder, Asperger disorder or PDD-NOS made by psychiatric interview and informed by the ADI-R and ADOS-G **Exclusion criteria:** Children were excluded if they: were responding well to previous interventions; had only mild global severity; had a DSM-IV psychotic disorder; had a history of seizures; had any clinically significant medical illness; had been free of psychiatric medications at least 6 weeks prior to participation; were not currently receiving psychotropic medication or cognitive behavioural therapy
Interventions	**Experimental Intervention: Low dose liquid fluoxetine** (or matching placebo) **Delivery of intervention:** Delivered by blinded treating physician **Format or method of administration:** Oral administration **Intensity:** Final dose fluoxetine 2.4-20 mg/day (mean: 9.9 mg/day); final dose placebo 4.8-30 mg/day (mean: 10.8 mg/day)

	Duration of intervention: 8 weeks **Total duration of follow-up:** 20 weeks (8 week double-blind trial followed by 4-week washout and 8-week cross-over trial)
Outcomes	**Direct outcome:** **Core autism feature: Restricted interests and rigid and repetitive behaviours** (as measured by the Children's Yale-Brown Obsessive Compulsive Scale [CYBOCS] - Compulsions subscale) **Indirect outcome:** **Core autism feature: Overall autistic behaviours** (as measured by the Global Autism Composite Improvement [incorporating Clinical Global Impression-Improvement Scale Adapted to Global Autism, CGI-AD and change scores on the CYBOCS]
Study Design	RCT (with cross-over phase)
Source of funding	Orphan Products Division of the Food and Drug Administration Grant # FD-R-001520-01-03, NIH STAART Center of Excellence Grant #1U54 MM066673-01A1, NARSAD Young Investigator Award for Dr Novotny, and the Seaver Foundation. Lilly Research Laboratories provided liquid fluoxetine and matching placebo for the study
Limitations	1. Risk of selection bias is unclear/unknown as the randomisation method is unclear and there is insufficient detail reported with regards to allocation concealment 2. Risk of selective reporting bias is unclear/unknown as there are no outcomes listed on ClinicalTrials.gov 3. High risk of other bias due to potential conflict of interest as the study drugs were provided by Lilly Research Laboratories
Notes	This study is registered on ClinicalTrials.gov, Study NCT00004486. Efficacy data extracted for phase 1 - the initial double-blind trial and not for the cross-over period as the 4-week washout period did not allow for complete elimination of the metabolite. Data could not be extracted for the adverse events. Two global measures were reported, the CGI-AD which measured global severity independently of the primary target of repetitive behaviours and the Global Autism Composite Improvement Measure which included both the target behaviour as well as other core symptoms. Data were extracted for the latter and not the former measure as it was more equivalent to how other trials have used the CGI-I measure.

1.4.2 KING2009

Study ID	KING2009
Bibliographic reference	King BH, Hollander E, Sikich L, McCracken JT, Scahill L, Bregman JD, et al. Lack of efficacy of citalopram in children with autism spectrum disorders and high levels of repetitive behavior: citalopram ineffective in children with autism. Archives of General Psychiatry. 2009;66:583-590.
Methods	**Allocation:** Randomised **Matching:** Stratified randomisation based on site and age **Blindness:** Intervention administrators, participants and outcome assessors were blind (though some outcome measures based on parent-report which was non-blind to other potentially confounding factors) **Setting:** Outpatient **Raters:** Clinician- and parent-rated **Country:** USA
Participants	**Diagnosis:** DSM-IV-TR autistic disorder, Asperger disorder or PDD-NOS **Coexisting conditions:** Participants had high levels of repetitive behaviours **Qualifying Diagnostic Assessment:** Clinical diagnosis informed by the Autism Diagnostic Interview-Revised (ADI-R) and the Autism Diagnostic Observation Schedule (ADOS) **N:** 149 **Age:** 5-17 years (mean: 9.4 years) **Sex:** 14% female **Ethnicity:** 72% white **IQ:** Not reported (58% IQ>70) **Inclusion criteria:** Children were included if they: were aged 5-17 years old; had a DSM-IV-TR diagnosis of autistic disorder, Asperger disorder or PDD-NOS made by an experienced clinician and informed by the ADI-R and ADOS; scored at least 'moderate' on the Clinical Global Impressions - Severity scale; scored >=8 for compulsive behaviours on the Children's Yale-Brown Obsessive Compulsive Scales modified for pervasive developmental disorders (CYBOCS-PDD) **Exclusion criteria:** Children were excluded if they: had Rett disorder or childhood disintegrative disorder or a history of bipolar disorder or manic episode; had a seizure within the past 6 months; had a medical condition that might interfere with study participation; weighed less than 15kg; had clinically significant abnormal baseline laboratory test results; had a history of adverse events; failed treatment while taking >=2 SSRIs; had previously been treated with citalopram or escitalopram oxalate; had recently started behavioural therapy; were currently taking any psychotropic medications (with the exception of melatonin or diphenhydramine hydrochloride for sleep) or medication with known interactions with citalopram
Interventions	**Experimental Intervention: Liquid citalopram** (Celexa, 10mg/5mL) or placebo (matched for smell, taste and viscosity) **Delivery of intervention:** Delivered by clinician **Format or method of administration:** Oral **Intensity:** 2.5-20mg/day (final dose mean: 16.5mg/day for citalopram; 18.5mg/day for placebo) **Duration of intervention:** 12 weeks **Total duration of follow-up:** 12 weeks

Outcomes	**Direct outcome:** **Core autism feature: Restricted interests and rigid and repetitive behaviours** (as measured by dichotomous measures of positive treatment response ['much improved/very improved' on CGI-improvement; and 'much improved/very improved' on CGI-improvement together with >25% improvement on Children's Yale-Brown Obsessive Compulsive Scales-PDD [CYBOCS-PDD]]; the CYBOCS-PDD compulsions score; and the Repetitive Behavior Scale [RBS] - Compulsive, Restrictive, Ritualistic, Sameness, Self-injurious and Stereotyped subscales) **Indirect outcomes:** **Behaviour that challenges** (as measured by the Aberrant Behaviour Checklist [ABC] - Irritability & Agitation, Lethargy & Social Withdrawal, Hyperactivity & Noncompliance, Stereotypic Behaviour and Inappropriate Speech subscales) **Adverse events** (as measured by dichotomous measures of any side effect and number of participants who experienced nightmares during treatment period)
Study Design	RCT
Source of funding	National Institutes of Health via the following STAART center contracts: Mount Sinai School of Medicine, New York, New York: U54-MH066673, Eric Hollander,MD,principal investigator (PI); University of North Carolina at Chapel Hill: U54-MH066418, Joseph Piven, MD, PI; University of California at Los Angeles: U54-MH068172, Marian Sigman, PhD, PI; Yale University, NewHaven, Connecticut: U54-MH066494, Fred Volkmar, MD, PI. Dartmouth Medical School, Hanover, New Hampshire, and Boston University, Boston, Massachusetts:U54-MH066398, Helen Tager-Flusberg, PhD, PI; and DM-STAT, Inc, Boston: U01-HD045023, Kimberly Dukes, PhD, PI. All of the study medications were purchased using National Institutes of Health grant funds.
Limitations	1. Risk of selection bias is unclear/unknown as the randomisation method is unclear and there is insufficient detail reported with regards to allocation concealment. 2. High risk of selective reporting bias as no data reported for the Parent Chief Complaint, Child and Adolescent Symptom Inventory: Anxiety and Depression scales, Behavioral Activation, Caregiver Strain Questionnaire or the Vineland Adaptive Behavior Scale which are listed as secondary outcomes on ClinicalTrials.gov 3. High risk of other bias due to potential conflict of interest as study authors are consultants to pharmaceutical companies
Notes	This trial is registered on ClinicalTrials.gov, Study NCT00086645. Authors contacted regarding missing outcome data but no reply.

1.4.3 LUBY2006

Study ID	LUBY2006
Bibliographic reference	Luby J, Mrakotsky C, Stalets MM, Belden A, Heffelfinger A, Williams M, et al. Risperidone in preschool children with autistic spectrum disorders: an investigation of safety and efficacy. Journal of Child and Adolescent Psychopharmacology. 2006;16:575-587.
Methods	**Allocation:** Randomised **Matching:** No matching **Blindness:** Parents and outcome assessors blinded but intervention administrator was non-blind **Setting:** Psychiatric outpatient clinic **Raters:** Clinician-rated **Country:** USA
Participants	**Diagnosis:** DSM-IV autism or PDD-NOS **Coexisting conditions:** None reported **Qualifying Diagnostic Assessment:** Not reported **N:** 24 (N=1 excluded post-randomisation but pre-intervention as did not meet threshold for ASD on the Childhood Autism Rating Scale [CARS] or the Gilliam Autism Rating Scale [GARS] so N=23 for demographics and analysis) **Age:** 2.5-6 years (mean: 4 years) **Sex:** 26% female **Ethnicity:** 92% white **IQ:** Not reported **Inclusion criteria:** Participants were included if they met DSM-IV criteria for autism or PDD-NOS), previously diagnosed and referred by a clinician **Exclusion criteria:** Other known significant central nervous system (CNS) disorders and significant medical problems or other psychiatric disorders requiring pharmacotherapy
Interventions	**Experimental Intervention: Risperidone** **Delivery of intervention:** Non-blind child psychiatrist **Format or method of administration:** Not reported **Intensity:** 0.5-1.5mg/day (means: 1.14mg/day for risperidone; 1.38mg/day for placebo) **Duration of intervention:** 24 weeks **Total duration of follow-up:** 24 weeks
Outcomes	**Direct outcome:** **Core autism feature: Overall autistic behaviours** (as measured by the Childhood Autism Rating Scale [CARS] - Total score) **Indirect outcomes:** **Adverse events: Weight gain** (as measured in kg); **Leptin change** (as measured in mg/L); and **Prolactin change** (as measured in ng/ml)
Study Design	RCT
Source of funding	Janssen Pharmaceutica
Limitations	1. High risk of selection bias as the allocation was unconcealed and the groups were not comparable at baseline (the risperidone group showed significantly greater severity of autism symptoms as measured by the CARS and significantly poorer language skills as measured by the PLS-3 and poorer motor skill development as measured by the VABS Motor Skills Scale)

	2. High risk of performance bias as the intervention administrator was non-blind to group assignment 3. High risk of selective reporting bias as no post-intervention outcomes were reported for: the Gilliam Autism Rating Scale (GARS); the Vineland Adaptive Behavior Scales (VABS); the Childhood Behavior Checklist 1.5-5 (CBCL); or the Preschool Language Scale, 3rd ed. (PLS-3) 4. High risk of other bias due to conflict of interest as the study was funded by the pharmaceutical company that manufactured the drug tested
Notes	Author contacted regarding missing outcome data but email bounced back

1.4.4 MIRAL2008

Study ID	MIRAL2008
Bibliographic reference	Miral S, Gencer O, Inal-Emiroglu FN, Baykara B, Baykara A, Dirik E. Risperidone versus haloperidol in children and adolescents with AD. European Child and Adolescent Psychiatry. 2008;17:1-8.
Methods	**Allocation:** Randomised **Matching:** No matching **Blindness:** Paper states 'Double-blind' but gives no further detail with regards to who is blinded, i.e. participant, parent, investigator, intervention administrator, outcome assessor **Setting:** Not reported **Raters:** Clinician-rated **Country:** Turkey
Participants	**Diagnosis:** DSM-IV Autistic Disorder **Coexisting conditions:** None reported **Qualifying Diagnostic Assessment:** Diagnosis based on consensus of two child psychiatrists **N:** 30 **Age:** 7-17 years (mean: 10.5 years) **Sex:** 17% female **Ethnicity:** Not reported **IQ:** Not reported **Inclusion criteria:** A DSM-IV diagnosis of autistic disorder; aged 8–18 years; have parental informed consent; and agree to be followed-up **Exclusion criteria:** Children were excluded from the study if they: also had epilepsy; had a concomitant neuropsychiatric illness (such as attention deficit and hyperactivity disorder, Tourette syndrome, etc.); demonstrated a psychotic disorder or symptoms; or had other PDDs.
Interventions	**Experimental Intervention: Risperidone** **Control Intervention: Haloperidol** **Delivery of intervention:** Not reported **Format or method of administration:** Not reported **Intensity:** Risperidone: 1.2-4mg/day (mean: 2.6mg/day); Haloperidol: 1-5.7mg/day (mean: 2.6mg/day) **Duration of intervention:** 10 weeks **Total duration of follow-up:** 12 weeks (including a 1-2 week screening phase)
Outcomes	**Direct outcome:** **Core autism feature: Overall autistic behaviours** (as measured by the Ritvo-Freeman Real Life Rating Scale [RF-RLRS) - Social, Motor, Affective, Sensory, and Language subscales; and the Turgay DSM-IV PDD Rating Scale) **Indirect outcomes:** **Behaviour that challenges** (as measured by the Aberrant Behavior Checklist [ABC] - Total score) **Adverse events: Extrapyramidal symptoms** (as measured by Chouinard Extrapyramidal Symptoms Rating Scale [ESRS] - Section I); **liver problems** (as measured by change in alanine transaminase [ALT]); and **prolactin levels** (as measured by prolactin concentration [ng/ml] change scores)
Study Design	RCT

Source of funding	Janssen and Cilag Drug Company
Limitations	1. High risk of selection bias due to unclear randomisation method and insufficient detail reported with regards to allocation concealment. There were also no baseline statistical comparisons between groups reported. 2. The risk of performance bias is unclear/unknown as the paper states 'Double-blind' but gives no further detail with regards to who is blinded, i.e. participant, investigator, intervention administrator 3. The risk of detection bias is unclear/unknown as the paper states 'Double-blind' but gives no further detail with regards to who is blinded, i.e. parent, outcome assessor. It is also unclear if follow-up duration of 12 weeks is sufficient to detect significant treatment effects, in particular, adverse events 4. The risk of selective reporting bias is unclear/unknown as the trial protocol is not registered on ClinicalTrials.gov 5. High risk of other bias due to conflict of interest as the study was partly funded by the pharmaceutical company that manufactured the drug tested
Notes	Not applicable

1.4.5 NAGARAJ2006

Study ID	NAGARAJ2006
Bibliographic reference	Nagaraj R, Singhi P, Malhi P. Risperidone in children with autism: randomized, placebo-controlled, double-blind study. Journal of Child Neurology. 2006;21:450-455.
Methods	**Allocation:** Randomised **Matching:** No matching **Blindness:** Participants, parents and outcome assessors were all blind to group assignment **Setting:** Outpatient **Raters:** Clinician-rated **Country:** India
Participants	**Diagnosis:** DSM-IV autism **Coexisting conditions:** None reported **Qualifying Diagnostic Assessment:** Diagnosis was established by two independent clinical observers, including a clinical psychologist **N:** 40 (however, N=1 dropped out of placebo group and demographic and efficacy data reported for N=39) **Age:** 2-9 years (mean: 5 years) **Sex:** 13% female **Ethnicity:** Not reported **IQ:** Not reported (28% with mild LD; 28% with moderate LD) **Inclusion criteria:** Consecutive referrals with varying symptoms, including hyperactivity, aggression, stereotypies, and language difficulties, with a maximum age of 12 years, and diagnosed with autism according to the DSM-IV criteria. **Exclusion criteria:** Participants were excluded if: they had severe LD; any significant coexisting disease or illness (neurologic, cardiovascular, respiratory, genetic); or severe malnutrition (weight for age < 60% of National Center for Health Statistics median)
Interventions	**Experimental Intervention: Risperidone** **Delivery of intervention:** Parents administered the dose at bedtime **Format or method of administration:** Oral administration of risperidone or placebo in liquid suspension form **Intensity:** 0.5mg/day for first 2 weeks and then 1mg/day for remaining 24 weeks **Duration of intervention:** 26 weeks **Total duration of follow-up:** 26 weeks
Outcomes	Direct outcome: **Core autism feature: Overall autistic behaviours** (as measured by a dichotomous measure of positive treatment response [>20% improvement on Childhood Autism Rating Scale]; and global state as measured by a dichotomous measure of positive treatment response [>20% improvement on Children's Global Assessment Scale]) **Indirect outcomes:** **Adverse events: Weight gain** (as measured in kg)
Study Design	RCT
Source of funding	Department of Pediatrics, Advanced Pediatric Centre, Postgraduate Institute

	of Medical Education and Research, Sector 12, Chandigarh, India
Limitations	1. High risk of selective reporting bias as mean and standard deviation data were not reported for continuous scale outcome measures and no data were reported for the Vineland Social Maturity Scale (VSMS) or the Abnormal Involuntary Movements Scale (AIMS) 2. The risk of other bias is unclear/unknown due to a potential conflict of interest as drugs were provided by the pharmaceutical company that manufactured them
Notes	Contacted author regarding continuous measure outcomes and missing outcome data but no reply

1.5 CHARACTERISTICS OF EXCLUDED PHARMACOLOGICAL INTERVENTION STUDIES

1.5.1 BELSITO2001

Reason for exclusion	Data could not be extracted as no measure of variability was reported

1.5.2 CARRASCO2012

Reason for exclusion	Systematic review with no new useable data and any meta-analysis results not appropriate to extract

1.5.3 CHEZ2003

Reason for exclusion	Non-randomised group assignment (participants were alternately assigned in the order they enrolled)

1.5.4 DOVE2012

Reason for exclusion	Systematic review with no new useable data and any meta-analysis results not appropriate to extract

1.5.5 DOYLE2012

Reason for exclusion	Non-systematic review

1.5.6 HURWITZ2012

Reason for exclusion	Systematic review with no new useable data and any meta-analysis results not appropriate to extract

1.5.7 KHALIL2012

Reason for exclusion	Non-systematic review

1.5.8 KOHLER1987

Reason for exclusion	Drug withdrawn from market due to significant safety concerns

1.5.9 KOLEVZON2006

Reason for exclusion	Systematic review with no new useable data and any meta-analysis results not appropriate to extract

1.5.10 MOORE2004

Reason for exclusion	Systematic review with no new useable data and any meta-analysis results not

	appropriate to extract

1.5.11 OBERMAN2012

Reason for exclusion	Non-systematic review

1.5.12 RAJAPAKSE2010

Reason for exclusion	Systematic review with no new useable data and any meta-analysis results not appropriate to extract

1.5.13 REMINGTON2001

Reason for exclusion	Data cannot be extracted due to cross-over design and unavailability of either first phase data or results of paired-sample t-tests. The population was also indirect due to mixed adult and children sample. Author contacted requesting both disaggregated and first phase data but not able to provide this information

1.5.14 SIEGEL2012A

Reason for exclusion	Systematic review with no new useable data and any meta-analysis results not appropriate to extract

1.5.15 SIEGEL2012B

Reason for exclusion	Non-systematic review

1.5.16 THEOHARIDES2012

Reason for exclusion	Non-systematic review

1.5.17 WILLIAMS2010

Reason for exclusion	Systematic review with no new useable data and any meta-analysis results not appropriate to extract

1.6 REFERENCES OF EXCLUDED PHARMACOLOGICAL INTERVENTION STUDIES

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1.7 CHARACTERISTICS OF INCLUDED BIOMEDICAL INTERVENTION STUDIES

1.7.1 ADAMS2009A/2009B

Study ID	ADAMS2009A/2009B
Bibliographic reference	Adams JB, Baral M, Geis E, Mitchell J, Ingram J, Hensley A, et al. Safety and efficacy of oral DMSA therapy for children with autism spectrum disorders: part A-medical results. BMC Clinical Pharmacology. 2009a;9:16. Adams JB, Baral M, Geis E, Mitchell J, Ingram J, Hensley A, et al. Safety and efficacy of oral DMSA therapy for children with autism spectrum disorders: part B - behavioral results. BMC Clinical Pharmacology. 2009b;9:17.
Methods	**Allocation:** Randomised **Matching:** No matching **Blindness:** Investigator, participants and carers were blinded **Setting:** Outpatient **Raters:** Parent-rated **Country:** USA
Participants	**Diagnosis:** ASD (diagnostic classification system not reported; for completers [N=41] and based on Autism Diagnostic Observation [ADOS] criteria 81% met criteria for Autism, 12% for ASD and 7% did not meet criteria for ASD) **Coexisting conditions:** None reported **Qualifying Diagnostic Assessment:** None reported **N:** 49 were randomised (Phase 2); 82 participants enrolled for Phase 1 and N=77 completed the initial blood draw and received screening phase round of drug. Demographic and outcome data could only be extracted for completers of Phase 2 (N=41) **Age:** Range not reported but inclusion criteria 3-8 years (mean: 6.6 years) **Sex:** 7% female **Ethnicity:** Not reported **IQ:** Not reported **Inclusion criteria:** Children were included into Phase 1 (screening round) if they: had a previous diagnosis (diagnostic classification system not reported) of ASD (made by a psychiatrist, psychologist or developmental paediatrician), the ADOS was administered in the present study but failing to meet ADOS criteria for ASD was not an exclusion criteria; were aged 3-8 years; had been taking multi-vitamin/mineral supplement with at least the RDA of zinc for at least 2 months prior to the start of the study and continued to do so for the trial duration; were well-hydrated (received adequate daily intake of water). Children were included into Phase 2 (randomised, double-blind, placebo-controlled phase) if they: excreted high amounts of toxic metals in Phase 1 (above Doctor's Data reference range, defined as the top 95% for typically developing children who are not undergoing chelation therapy); had normal kidney/liver function, serum transaminases, and Complete Blood Count (CBC) (based on a blood test); had no changes made to the medication, supplements, diet, or behavioral interventions received during the study; continued to stay well-hydrated. **Exclusion criteria:** Children were excluded from both phases if they had: mercury amalgam dental fillings; previously used DMSA or other prescription

	chelators; anaemia or were currently being treated for anaemia due to low iron; a known allergy to DMSA; liver or kidney disease
Interventions	**Experimental Intervention: Long-term chelation (7-rounds of Dimercaptosuccinic Acid [DMSA] therapy).** Following baseline assessment, parents administered a lotion containing glutathione (and isopropyl myristate, mineral oil, caprylic/capric trigliceride, and vitamin E acetate) once a day for 7 days (after bath on clean skin with child rubbing it on). After 7 days of the lotion, participants received one screening round of DMSA (a round consisted of 3 doses/day for 3 days, followed by 11 days off). DMSA was compounded individually for each child from pharmaceutical grade DMSA (over 99% pure) supplied by Spectrum Chemical. Children who met criteria for Phase 2 (in particular those excreting significant heavy metals) continued on to Phase 2 where they were randomised to received continued DMSA or placebo, and in the former case received 6 subsequent rounds of DMSA. **Control Intervention: Short-term chelation (1-round of DMSA therapy and 6-rounds of placebo).** Following baseline assessment, parents administered a placebo lotion (matched to glutathione in packaging and formulation) once a day for 7 days (after bath on clean skin with child rubbing it on). After 7 days of the lotion, participants received one screening round of DMSA (a round consisted of 3 doses/day for 3 days, followed by 11 days off). Children who met criteria for Phase 2 (in particular those excreting significant heavy metals) continued on to Phase 2 where they were randomised to continued DMSA or placebo, and in the latter case received 6 subsequent rounds of placebo (methyl cellulose). To control for the strong smell of DMSA the bottles of placebo included a small slotted container that contained DMSA so that the medication smell was present. **Delivery of intervention:** Identity of intervention administrator not reported **Format or method of administration:** Oral administration **Intensity:** Actual intensity not reported but planned intensity for the experimental group was 180mg/day (l-glutathione) and 7 rounds of DMSA (each round consists of 3 days of DMSA [10 mg/kg-dose, 9 doses over 3 days], followed by 11 days off [no treatment], and then repeating). For the control group 1 round of DMSA and 6 rounds of placebo received. **Duration of intervention:** 17 weeks **Total duration of follow-up:** 17 weeks
Outcomes	**<u>Direct outcome:</u>** **Core autism feature: Overall autistic behaviours** (as measured by Autism Evaluation Treatment Checklist [ATEC] - Total score, and Speech/Language/Communication, Sociability, Sensory/Cognitive Awareness, and Health/Physical/Behavior subscales; Pervasive Development Disorder Behavior Inventory [PDDBI] - Autism Composite score; and Severity of Autism Scale [SAS] - Total score) **<u>Indirect outcomes:</u>** **Core autism features: Impaired reciprocal social communication and interaction** (as measured by PDDBI - Social Pragmatic, and Social Approach subscales); **Restricted interests and rigid and repetitive behaviours** (PDDBI - Sensory/Perceptual Approach Behaviours; and Ritualisms/Resistance to Change subscales) **Behaviour that challenges** (as measured by PDDBI - Maladaptive Behaviours Composite score, and Arousal Regulation Problems, and Aggressiveness subscales)

	Coexisting problems or disorders: Adaptive behaviour (as measured by PDDBI - Adaptive Behaviours Composite score); **Speech and language** (as measured by PDDBI - Semantic Pragmatic Problems, Expressive Language, and Learning, Memory, and Receptive Language subscales); and **Anxiety** (as measured by PDDBI - Specific Fears subscale)
Study Design	RCT
Source of funding	Wallace Foundation and the Autism Research Institute
Limitations	1. Risk of selection bias is unclear/unknown as the randomisation method is unclear, insufficient detail reported with regards to allocation concealment, and group comparability at baseline is unclear 2. High risk of selective reporting bias as efficacy data cannot be extracted for the ADOS Communication, Sociability, and Communication+Sociability or the Parent Global Impressions scale as no measure of variability reported. Data can also not be extracted for adverse events as although number of dropouts is reported the original group assignment sample sizes are unclear 3. High risk of other bias due to potential conflict of interest as DMSA provided by manufacturer
Notes	Trial protocol is registered on ClinicalTrials.gov, Study ID NCT00811083. Contacted author regarding missing outcome data but no reply

1.7.2 ADAMS2011

Study ID	ADAMS2011
Bibliographic reference	Adams JB, Audhya T, McDonough-Means S, Rubin RA, Quig D, Geis E, et al. Effect of a vitamin/mineral supplement on children and adults with autism. BMC Pediatrics. 2011;11:111.
Methods	**Allocation:** Randomised **Matching:** No matching **Blindness:** Parents (who were intervention administrators and outcome assessors), participants and study staff (nurses, physician, laboratory staff and PI) were blinded **Setting:** Outpatient **Raters:** Parent-rated and nurse-rated **Country:** USA
Participants	**Diagnosis:** ASD (diagnostic classification system not reported; 80% autism, 10% Asperger's disorder and 11% PDD-NOS) **Coexisting conditions:** None reported **Qualifying Diagnostic Assessment:** No diagnostic assessment was performed for the study **N:** 141 **Age:** Range not reported but inclusion criteria 3-60 years (mean: 10.8 years) **Sex:** 11% female **Ethnicity:** Not reported **IQ:** Not reported **Inclusion criteria:** Children were included if they: were aged 5-16 years for the Arizona group or 3-60 years for the National group; had a prior diagnosis (with written verification) of PDD-NOS or Asperger's disorder made by a psychiatrist or similar professional (no diagnostic assessment performed for the study); had not used a vitamin or mineral supplement in the last 2 months; had not changed medical, dietary, behaviour, or other treatment in the last two months and showed a willingness to avoid any changes for the study duration; were not currently using any chelation intervention **Exclusion criteria:** Not reported
Interventions	**Experimental Intervention: Multivitamin and mineral supplement.** The supplement included most vitamins and minerals with the exception of vitamin K, copper and iron) and was provided as a liquid (with a cherry flavour). Dosage levels of nutrients in the supplement were selected to be significantly higher than RDA levels, but either at or below the Tolerable Upper Limit **Delivery of intervention:** Delivered by parent or school staff **Format or method of administration:** Oral administration **Intensity:** One dose a day at lunchtime (formulation of vitamin/mineral supplement based on 60lb which was adjusted up or down according to body weight up to a maximum of 100lb: 1000 IU vitamin A; 600mg vitamin C; 300 IU vitamin D3; 150 IU vitamin E; 70mg mixed tocopherols; 20mg B1, 20mg B2, 15mg niacin and 10mg niacinamide B3; 15mg B5; 40mg B6; 500mcg B12; 100mcg folic acid; 550mcg folinic acid; 150mcg biotin; 250mcg choline; 100mcg inositol; 3.6mg mixed carotenoids; 50mg coenzyme Q10; 50mg N-acetylcysteine; 100mg calcium; 70mcg chromium; 100mcg iodine; 500mcg lithium; 100mg magnesium; 3mg manganese; 150mcg molybdenum; 50mg

	potassium; 22mcg selenium; 500mg sulfur; 12mg zinc) **Duration of intervention:** 13 weeks **Total duration of follow-up:** 13 weeks
Outcomes	**Direct outcome:** **Core autism feature: Overall autistic behaviours** (as measured by Parent Global Impressions-Revised [PGI-R] - Overall improvement subscale or Average improvement [average of all subscales]; Autism Evaluation Treatment Checklist [ATEC] - Total score; Severity of Autism Scale [SAS] - Total score; and Pervasive Development Disorder Behavior Inventory [PDDBI] - Total score) **Indirect outcomes:** **Core autism feature: Impaired reciprocal social communication and interaction** (as measured by the PGI-R - Sociability improvement and Eye contact improvement subscales) **Behaviour that challenges** (as measured by PGI-R - Hyperactivity improvement and Tantrumming improvement subscales) **Coexisting problems or disorders: Speech and language** (as measured by PGI-R - Receptive language improvement and Expressive language improvement subscales); **IQ** (as measured by PGI-R - Cognition improvement subscale); **Sleep** (as measured by PGI-R - Sleep improvement subscale); and **gastrointestinal symptoms** (as measured by PGI-R - GI improvement subscale) **Adverse events** (as measured by dichotomous measures of: Discontinuation due to adverse events; Discontinuation due to diarrhoea; Discontinuation due to increased stimming and Discontinuation due to behaviour problems)
Study Design	RCT
Source of funding	Autism Research Institute and the Legacy Foundation
Limitations	1. Risk of selection bias is unclear/unknown as randomisation method is unclear and group comparability at baseline unclear 2. Risk of detection bias is different for different outcomes: Unclear/unknown for the Parent Global Impressions-Revised (PGI-R) scale as revised scale and no independent reliability and validity ratings and parent-rated so non-blind to other potentially confounding factors and Severity of Autism Scale (SAS) as reliability and validity of this outcome measure is unclear and parent-completed so non-blind 3. High risk of other bias due to potential conflict of interest as supplements provided by manufacturers for the study and first author receives free supplements from supplement manufacturers for personal use
Notes	Study performed in two groups: an Arizona group (who also participated in nutritional and metabolic status laboratory testing) and were a child-only sample (<=16 years) and a national sample which included adults and children (3-60 years). However, data are only presented for the combined groups. The authors were contacted for disaggregated (age<19 years) data but no reply so study will be downgraded on the basis of indirectness (population) as a result of the mixed child and adult sample. Trial protocol registered on ClinicalTrials.gov (Study ID NCT01225198)

1.7.3 BAHRAMI2012

Study ID	BAHRAMI2012
Bibliographic reference	Bahrami F, Movahedi A, Marandi SM, Abedi A. Kata techniques training consistently decreases stereotypy in children with autism spectrum disorder. Research in Developmental Disabilities. 2012;33:1183-1193.
Methods	**Allocation:** Randomised **Matching:** Matched on age, gender and autism severity **Blindness:** Non-blind **Setting:** Educational (specialist) **Raters:** Examiners (identity and blinding not reported) based on interview with carers and teachers **Country:** Iran
Participants	**Diagnosis:** DSM-IV ASD **Coexisting conditions:** Not reported **Qualifying Diagnostic Assessment:** None reported **N:** 30 **Age:** 5-16 years (mean; 9.1 years) **Sex:** 13% female **Ethnicity:** Not reported **IQ:** Not reported **Inclusion criteria:** Children were included if they: had a previous formal DSM-IV diagnosis of ASD; were attending an autism institute; were judged to be eligible for participating in Kata training after screening by an experienced physician **Exclusion criteria:** Not reported
Interventions	**Experimental Intervention: Kata exercise training.** Participants were trained in a modified form of Heian Shodan (shotokan) Kata techniques (including techniques from karate). Kata techniques which were trained included logical arrangements of blocking, punching, sticking, and kicking techniques in a set sequence. A number of autism-specific modifications were made to Kata training, including an initial 20-hour training course for instructors in autism, the use of video to model a specific technique at the beginning of each training session, and techniques to help keep participants engaged including reinforcement, inclusion of play activities, visual demonstration/modeling, visual cues (pictures, line, and spots drawings on the floor), and practice. **Delivery of intervention:** Intervention delivered by qualified and certified Kata trainers **Format or method of administration:** Individual **Intensity:** Actual intensity not reported but planned intensity estimated at 52 hours (56 sessions; 2 hours/week up to week 8 and 6 hours/week for weeks 9-14) **Duration of intervention:** 14 weeks **Total duration of follow-up:** 19 weeks (including one-month post-intervention follow-up)
Outcomes	**Direct outcome:** **Core autism feature: Restricted interests and rigid and repetitive behaviours** (as measured by Gilliam Autism Rating Scale [GARS] - Stereotyped behaviour subscale)
Study Design	RCT

Source of funding	Not reported
Limitations	1. Risk of selection bias is unclear/unknown as randomisation method is unclear and insufficient detail reported with regards to allocation concealment 2. High risk of performance bias as intervention administrators non-blind 3. High risk of response bias as participants non-blind 4. High risk of detection bias as outcome measure based on interview with carers and teachers who were non-blind and blinding of examiner not reported 5. Risk of selective reporting bias is unclear/unknown as trial protocol not registered on ClinicalTrials.gov or ISRCTN
Notes	Not applicable

1.7.4 CHAN2009

Study ID	CHAN2009
Bibliographic reference	Chan AS, Cheung M-C, Sze SL, Leung WW. Seven-star needle stimulation improves language and social interaction of children with autistic spectrum disorders. American journal of Chinese Medicine. 2009;37:495-504.
Methods	**Allocation:** Randomised **Matching:** No matching reported **Blindness:** No blinding of particants or care administrators reported. Outcome assessors were blind for measures that are not reported here, but all outcomes reported here were parent rated and parents were not blind to treatment allocation. **Setting:** Not reported **Raters:** Parents **Country:** China
Participants	**Diagnosis:** Autism Spectrum Disorder (classification system not reported) **Coexisting conditions:** No information about coexsisting conditions reported **Qualifying Diagnostic Assessment:** Not reported **N:** 32 **Age:** Range: Not reported (Mean: 6.87 years) **Sex:** 19% female **Ethnicity:** Not reported **IQ:** Range: not reported (Mean: 85.4) based on the Test of Nonverbal Intelligence **Inclusion criteria:** Not reported **Exclusion criteria:** Not reported
Interventions	**Experimental Intervention: Acupressure.** The intervention involved seven-star needle stimulation (without penetrating the skin) delivered using a dermatoneural medical hammer (with the head holding the seven blunt needles in the shape of a seven-point star) to various parts of the back, body and head **Delivery of intervention:** The sessions were delivered to the children on an individual basis by a therapist **Format or method of administration:** Individual **Intensity:** Children received 30 sessions of treatment (5 sessions a week for 6 weeks), each lasting a maximum of 10 minutes. A total of 5 hours. **Duration of intervention:** 6 weeks **Total duration of follow-up:** 6 weeks
Outcomes	**Direct Outcome** **Core autism feature: Overall autistic behaviours** (as measured by the study-specific parent-rated questionnaire - Total score and Language, Social interaction, Stereotyped behaviour, and Motor functioning subscales)
Study Design	RCT
Source of funding	A grant from Culture Homes Ltd
Limitations	1. Unclear risk of selection bias: Methods of randomisation and concealment of allocation are not reported 2. High risk of performance bias: Intervention administrators were non-blind 3. High risk of response bias: Participants were non-blind 4. High risk of detection bias: Outcomes were based on a study-specific

	questionnaire with no information on validity or reliability. Measures were parent-rated and parents were not blind to treatment allocation or confounding variables. 5. Unclear risk of selective reporting: All outcomes are reported but the study is not registered
Notes	Potential conflict of interest in funding as Culture Homes Ltd sell household items, along with medical supplies and equipment

1.7.5 CHEZ2002

Study ID	CHEZ2002
Bibliographic reference	Chez MG, Buchanan CP, Aimonovitch MC, Becker M, Schaefer K, Black C, et al. Double-blind, placebo-controlled study of L-carnosine supplementation in children with autistic spectrum disorders. Journal of Child Neurology. 2002;17:833-837.
Methods	**Allocation:** Randomised **Matching:** No matching **Blindness:** Participants, parents (who were also intervention administrators) and outcome assessors were blinded **Setting:** Outpatient **Raters:** Parent-rated or identity of outcome assessor not reported (but clinicians and neurologists involved in study were blinded) **Country:** USA
Participants	**Diagnosis:** DSM-IV-R ASD **Coexisting conditions:** None reported **Qualifying Diagnostic Assessment:** None reported **N:** 31 **Age:** 3-12 years (mean: 7.5 years) **Sex:** 32% female **Ethnicity:** Not reported **IQ:** Not reported **Inclusion criteria:** Children were included if: they were aged 3-12 years; had a prior DSM-IV-R diagnosis of PDD or autistic disorder **Exclusion criteria:** Children were excluded if they had a family history of: seizure disorder; fragile-X syndrome; other genetic disorder or etiology of their spectrum disorder
Interventions	**Experimental Intervention: L-carnosine supplement.** All pills were contained by a gelatin capsule and parents were instructed to mix the powder with food or drink **Delivery of intervention:** Intervention delivered by parents **Format or method of administration:** Oral administration **Intensity:** Actual intensity not reported but planned intensity was 800mg/day (in two daily doses of 400mg) **Duration of intervention:** 8 weeks **Total duration of follow-up:** 8 weeks
Outcomes	**Direct outcome:** **Core autism feature: Overall autistic behaviours** (as measured by the Parent Global Impressions-Improvement [PGI-I] - Overall improvement across subscales; the Childhood Autism Rating Scale [CARS] - Total score; and the Gilliam Autism Rating Scale [GARS] - Total score) **Indirect outcomes:** **Core autism features: Impaired reciprocal social communication and interaction** (as measured by GARS - Social interaction, and Communication subscales); **Restricted interests and rigid and repetitive behaviours** (as measured by GARS - Stereotyped behaviours subscale) **Coexisting problems or disorders: Speech and language** (as measured by the Expressive One Word Picture Vocabulary Test [EOWPVT] - raw score and age adjusted score; and the Receptive One-Word Picture Vocabulary Test

	[ROWPVT] - raw score and age adjusted score)
Study Design	RCT
Source of funding	Not reported
Limitations	1. Risk of selection bias is unclear/unknown as randomisation method is unclear and groups not comparable at baseline (significant baseline group difference [p=0.02] on the communication subscale of the Gilliam Autism Rating Scale with the experimental group showing greater severity [mean: 21.64] than the control group [mean: 15.23]) 2. Risk of selective reporting bias is unclear/unknown as the trial protocol is not registered on ClinicalTrials.gov or ISRCTN
Notes	Not applicable

1.7.6 CONIGLIO2001

Study ID	CONIGLIO2001
Bibliographic reference	Coniglio SJ, Lewis JD, Lang C, Burns TG, Subhani-Siddique R, Weintraub A, et al. A randomized, double-blind, placebo-controlled trial of single-dose intravenous secretin as treatment for children with autism. Journal of Pediatrics. 2001;138:649-655.
Methods	**Allocation:** Randomised **Matching:** No matching reported **Blindness:** Study reports a 'double-blind trial', but no information on who is blind is reported. **Setting:** Research setting and hospital **Raters:** Assessments were administered by 2 clinical psychologists, 1 developmental pediatrician and 1 advanced psychology graduate student **Country:** USA
Participants	**Diagnosis:** DMS-IV diagnosis of autism (51% autism; 19% PDD; 30% both autism and PDD) **Coexisting conditions:** No information on coexisting conditions reported, but children were only included if they had a language score of ≤60 on the Preschool Language Scale-3. **Qualifying Diagnostic Assessment:** Childhood Autsim Rating Scale (CARS) **N:** 60 **Age:** Range: not reported [Mean: 7 years] **Sex:** 25% female **Ethnicity:** 78% white **IQ:** Not reported **Inclusion criteria:** Children were included if they had: a DSM-IV diagnosis of autism; a score of >30 on the Childhood Autism Rating Scale (CARS); a language score of <60 months on the Preschool Language Scale-3 (PLS). **Exclusion criteria:** Not reported
Interventions	**Experimental Intervention: Porcine secretin** (Secretin-Ferring). **Control Intervention: Saline placebo** **Delivery of intervention:** Syringes were prepared by hospital pharmacists; no further information of care administrators reported. Children received injections individually. **Format or method of administration:** Intravenous (delivered using identical syringes) **Intensity:** 2 CU/kg (up to 75 CU) **Duration of intervention:** Single dose **Total duration of follow-up:** 6 weeks (assessments were done at two time-points; 3 weeks [post-intervention] and 6 weeks [follow-up])
Outcomes	**Direct Outcome** **Core autism feature: Overall autistic behaviours** (Dichotomous measure of positive treatment response as measured by number of participants showing a clinical improvement [decrease of <=4.07 points on CARS])
Study Design	RCT
Source of funding	Not reported
Limitations	1. Unclear risk of selection bias: methods of randomisation and concealment of allocation not reported and groups were not comparable at baseline on several

	variables including frequency of abnormal development from birth onwards, 3 of 15 (unspecified) characteristics of DSM-IV criteria for autism and PLS language age score 2. Unclear risk of detection bias: the study reports the trial was double-blind, but no information on who was blind was reported. As a placebo-controlled trial, can assume participants were blind, but unclear whether care administrators/outcome assessors were blind. 3. High risk of selective reporting: the study was not registered and not all data could be extracted (data could not be extracted for the CARS [continuous measure], GARS or PLS)
Notes	Contacted author regarding missing outcome data but no longer employed at correspondence address and could not find alternative contact details

1.7.7 DUNNGEIER2000

Study ID	DUNNGEIER2000
Bibliographic reference	Dunn-Geier J, Ho HH, Auersperg E, Doyle D, Eaves L, Matsuba C, et al. Effect of secretin on children with autism: a randomized controlled trial. Developmental Medicine and Child Neurology. 2000;42:796-802.
Methods	**Allocation:** Randomised **Matching:** Participants were matched by age and site **Blindness:** Participants, parents, care-administrators and outcome assessors were all blind to treatment allocation **Setting:** Not reported **Raters:** Parents and clinicians (no further details on clinicians reported) **Country:** Canada
Participants	**Diagnosis:** DSM-IV autism **Coexisting conditions:** Details on coexisting conditions not reported **Qualifying Diagnostic Assessment:** Diagnosis of autism was based on a score of ≥6 on the DSM-IV diagnostic criteria; semi-structured interview with the parents and a behaviour observation of the child leading to a score of ≥30 on Childhood Autism Rating Scale (CARS); clinical judgement of a psychologist and developmental pediatrician. **N:** 95 **Age:** Range: not reported (mean: 5.1 years) **Sex:** 7% female **Ethnicity:** 79% white **IQ:** Not reported **Inclusion criteria:** Children were included if they had a diagnosis of autism based on: a score of 6 and above on DSM-IV criteria for autism; parental interviews and behavioural observation of the child leading to a score of 30 and above on Childhood Autism Rating Scale (CARS); clinical judgement of a registered psychologist and developmental pediatrician. **Exclusion criteria:** Children were excluded if: they had previously used secretin; they had another genetic or neurological disorder (Rett syndrome, tuberous sclerosis); they had a disorder of the liver or pancreas; any treatment had started or changed in the 2 months preceding the start of the study; any treatment was due to begin within three weeks after the intervention had been administered
Interventions	**Experimental Intervention: Porcine secretin** **Control Intervention: Clear saline placebo** **Delivery of intervention:** Children received the intervention individually by a physician who was blind to the treatment allocation **Format or method of administration:** Intravenous delivered with an opaque syringe **Intensity:** 2 CU/kg secretin (up to 75 CU). The control group received the same dosage of saline. **Duration of intervention:** Single dose **Total duration of follow-up:** 3 weeks
Outcomes	**Direct Outcome** **Core autism feature: Overall autistic behaviours** (as measured by Childhood Autism Rating Scale [CARS]-Total score; Autism Behaviour Checklist [ABC]-Total score, and Sensory, Social relatedness, Body and object use, Language

	and Socialization subscales) **Indirect Outcome** **Coexisting problems or disorders: Speech and language** (as measured by Preschool Language Scale-3 [PLS-3]-Auditory comprehension and Expressive communication subscales); **Gastrointestinal symptoms** (as measured by parent-rated number of gastrointestinal problems)
Study Design	RCT
Source of funding	Grants from the Children's Hospital of Eastern Ontario Research Institute and the PA Woodward's Foundation
Limitations	1. Unclear risk of selective reporting: all outcomes are reported but the study is not registered
Notes	In order to ensure randomisation, concealment of allocation and blinding of care-administrators, an independent biostatistician generated the randomisation sequence, which was then kept at the pharmacy. When a child was ready for an injection, the study coordinator would inform the pharmacist, who would then prepare the approriate vial and pass this to the study coordinator who would pass it on the the physician. All outcomes are change scores. The authors were contacted to request endpoint scores, but no response received.

1.7.8 FAHMY2013

Study ID	FAHMY2013
Bibliographic reference	Fahmy SF, El-hamamsy MH, Zaki OK, Badary OA. L-Carnitine supplementation improves the behavioural symptoms in autistic children. Research in Autism Spectrum Disorder. 2013;7:159-166.
Methods	**Allocation:** Randomised **Matching:** No matching reported **Blindness:** Participants, parents and outcome assessors were blind to treatment allocation **Setting:** Outpatient **Raters:** Study investigator **Country:** Egypt
Participants	**Diagnosis:** Autism (diagnostic classification not reported) **Coexisting conditions:** Not reported **Qualifying Diagnostic Assessment:** Not reported **N:** 30 **Age:** Range 2.4-8.6 years (median: 5.7/5.8) **Sex:** 17% female **Ethnicity:** Not reported **IQ:** Not reported **Inclusion criteria:** Not reported **Exclusion criteria:** Not reported
Interventions	**Experimental Intervention: L-Carnitine** was administered to participants in liquid form, in the morning and evening. Dosing instructions were explained to parents by the pharmacist and printed on the packaging. Placebo matched on appearance and taste (containing 5% glucose syrup)

	Delivery of intervention: Intervention was delivered to children by their parents **Format or method of administration:** Oral (liquid form) **Intensity:** 100mg/kg a day in two doses (morning and evening) **Duration of intervention:** 26 weeks **Total duration of follow-up:** 26 weeks
Outcomes	**Direct outcome:** **Core autism feature: Overall autistic behaviour** (as measured by the Childhood Autism Rating Scale [CARS]: Total score)
Study Design	RCT
Source of funding	Not reported
Limitations	1. Risk of selection bias was unclear/unknown as insufficient detail was reported with regards to allocation concealment 2. Risk of selective reporting bias is unclear/unknown as trial protocol is not registered on ClinicalTrials.gov or ISRCTN 3. High risk of other bias due to potential conflict of interest as L-Carnitine was supplied by a company that sells the drug
Notes	Data were not extracted for free and total carnitine levels as outcomes outside scope

1.7.9 GRANPEESHEH2010

Study ID	GRANPEESHEH2010
Bibliographic reference	Granpeesheh D, Tarbox J, Dixon DR, Wilke AE, Allen MS, Bradstreet JJ. Randomized trial of hyperbaric oxygen therapy for children with autism. Research in Autism Spectrum Disorders. 2010;4:268-275.
Methods	**Allocation:** Randomised **Matching:** Matched on number of hours of ABA intervention they were receiving at the start of the study and age **Blindness:** Investigators, carers, participants and outcome assessors blinded. Intervention administrators non-blind **Setting:** Outpatient **Raters:** Paper describes outcome assessors as 'trained assessors who were blind to group assignment' but gives no further detail **Country:** USA
Participants	**Diagnosis:** DSM-IV Autistic disorder **Coexisting conditions:** None reported **Qualifying Diagnostic Assessment:** Diagnosis corroborated using the Autism Diagnostic Observation Schedule-Generic (ADOS-G) **N:** 46 (N=46 randomised but demographics and outcome data only reported for completers N=34) **Age:** Range not reported but inclusion criteria 2-14 years (mean: 6.2 years) **Sex:** Not reported **Ethnicity:** Not reported **IQ:** Not reported **Inclusion criteria:** Children were included if: they had a DSM-IV diagnosis of Autistic disorder corroborated using the ADOS-G; they were aged 2-14 years; English was the primary language spoken at home; they had access to Center for Autism & Related Disorders clinics as necessary for the study duration; their carer committed to completing 80 sessions in 10-15 weeks; their carer agreed not to introduce or alter any treatments during the study **Exclusion criteria:** Children were excluded if they: had previously received any hyperbaric oxygen treatment (HBOT); had received new dietary or biomedical treatment within 3 months prior to enrolment; had inadequate vision or hearing for the purposes of test administration; were non-ambulatory or required more than minimum support walking; had an unstable medical disorder; had a history of, or current seizure disorder; had a history of, or current asthma; had a history of, or current pulmonary cysts; had a history of, or current emphysema; had a history of, or current severe claustrophobia; had current otitis media; had current sinus infection; had current upper respiratory tract infection (URTI)
Interventions	**Experimental Intervention: Hyperbaric oxygen treatment (HBOT).** Participants were delivered 1.3 atmosphere (atm) and 24% oxygen in a HBOT chamber (Vitaeris 320 inflatable chamber, OxyHealth, Inc.) **Control Intervention: Attention-placebo condition.** Participants provided with free airflow through the HBOT chamber at ambient pressure **Delivery of intervention:** Identity of intervention administrator not reported **Format or method of administration:** Individual **Intensity:** Actual intensity not reported but planned intensity was 80 hours (6-10 hours/week)

	Duration of intervention: 10-15 weeks **Total duration of follow-up:** 34 weeks (ClinicalTrials.gov reports 1-month and 3-month follow-ups but paper does not report follow-up data)
Outcomes	**Direct outcomes:** **Core autism features: Impaired reciprocal social communication and interaction** (as measured by dichotomous measures of positive treatment response [improvement in ADOS Communication and improvement in ADOS Socialization]; and the Social Responsiveness Scale [SRS] - Social Awareness [change score]; Social Cognition [change score]; Social Communication [change score]; Social Motivation [change score]; Autistic Mannerisms [change score] subscale; and a behavioural observation measure of Appropriate vocalization [change score]) **Indirect outcomes:** **Core autism feature: Overall autistic behaviours** (as measured by dichotomous measure of positive treatment response [improvement in ADOS Total score]); **Restricted interests and rigid and repetitive behaviours** (as measured by behavioural observations of Vocal stereotypy [change score] and Physical stereotypy [change score]) **Behaviour that challenges** (as measured by behavioural observations of Challenging behaviours [change score] and Hyperactivity [change score]) **Coexisting problems or disorders: Adaptive behaviour** (as measured by the Vineland Adaptive Behaviour Scale [VABS] - Adaptive Composite [change score] and Communication [change score], Daily Living Skills [change score], and Socialization [change score] subscales); **Speech and language** (as measured by the Peabody Picture Vocabulary Test, 3rd Ed. [PPVT-III] - Total [change score])
Study Design	RCT
Source of funding	OxyHealth, Inc. (provision of chambers), The International Child Development Resource Center, and the Center for Autism and Related Disorders, Inc.
Limitations	1. Risk of selection bias is unclear/unknown as insufficient detail reported with regards to allocation concealment and groups were not comparable at baseline (statistically significant baseline group difference in ABC Irritability and RBS Self-injurious behaviour with higher scores in the control group) 2. High risk of performance bias as intervention administrator non-blind 3. Risk of attrition bias is unclear/unknown as N=12 dropped out but the paper does not report the groups these participants were assigned to 4. High risk of selective reporting bias as data cannot be extracted for the Aberrant Behavior Checklist (ABC), the Repetitive Behavior Scale (RBS), the Clinical Global Impression-Severity (CGI-S) scale or the Parent Stress Index (PSI). Moreover, for all outcomes the paper does not report results for post-intervention follow-up 5. High risk of other bias due to potential conflict of interest as equipment provided by manufacturer and one of the authors owns a centre which provides hyperbaric oxygen treatment services
Notes	Trial protocol registered on ClinicalTrials.gov, Study ID NCT00404846. Contacted author regarding missing outcome data and endpoint data but no reply.

1.7.10 KNIVSBERG2002/2003

Study ID	KNIVSBERG2002/2003
Bibliographic reference	Knivsberg AM, Reichelt KL, Høien T, Nødland M. A randomised, controlled study of dietary intervention in autistic syndromes. Nutritional Neuroscience. 2002;5:251-261. Knivsberg AM, Reichelt KL, Høien T, Nødland M. Effect of dietary intervention on autistic behavior. Focus on Autism and Other Developmental Disabilities. 2003;18:247-256.
Methods	**Allocation:** Randomised **Matching:** Matched on severity of autistic symptoms, age and PIQ **Blindness:** Investigator (outcome assessor) is blinded but parents (who are also intervention administrators) and participants non-blind **Setting:** Home **Raters:** Investigator (based on parental interview) or not reported **Country:** Norway
Participants	**Diagnosis:** Autism (diagnostic classification system not reported) **Coexisting conditions:** None reported **Qualifying Diagnostic Assessment:** None reported (prior diagnosis made by independent child psychiatry/neurology professionals) **N:** 20 **Age:** 4-10 years (mean: 7.4 years) **Sex:** Not reported **Ethnicity:** Not reported **IQ:** FIQ or VIQ not reported. PIQ: 35-144 (mean: 82.8, assessed with the Leiter International Performance Scale; 39% of N=18 with data had LD [PIQ<70]) **Inclusion criteria:** Children were included if they had: a diagnosis of autism (diagnostic classification system not reported) made by independent child psychiatry/neurology professionals; abnormal urinary peptide patterns (based on blinded analysis of urine samples) **Exclusion criteria:** Not reported
Interventions	**Experimental Intervention: Gluten-free and casein-free diet.** A dietician visited parents and provided oral and written information about gluten-free and casein-free diets. Parents were also able to contact the dietician by telephone during the trial period. **Delivery of intervention:** Parents delivered intervention **Format or method of administration:** Parent training **Intensity:** Unknown (compliance not recorded) **Duration of intervention:** 52 weeks **Total duration of follow-up:** 52 weeks
Outcomes	**Direct outcome:** **Core autism feature: Overall autistic behaviours** (as measured by Diagnose of Psykotisk Adferd hos Børn, DIPAB [Diagnosis of Psychotic Behaviour in Children] - Total score) **Indirect outcomes:** **Core autism features: Impaired reciprocal social communication and interaction** (as measured by DIPAB - Communication and interaction [K-scores]; Resistance to communication and interaction [M-scores]; and Social interaction or isolation [I-scores[]); **Restricted interests and rigid and**

	repetitive behaviours (as measured by DIPAB - Unusual or bizarre behaviour [B-scores]) **Coexisting problems or disorders: Fine and gross motor skills** (as measured by Movement Assessment Battery for Children -Test of Motor Impairment [TOMI])
Study Design	RCT
Source of funding	County council of Rogaland, Sigval and Nanki Bergesen's public trust, and the Seim Family Foundation
Limitations	1. Risk of selection bias is unclear/unknown as randomisation method is unclear 2. High risk of performance bias as intervention administrators were non-blind parents 3. High risk of response bias as participants were non-blind 4. Risk of detection bias is different for different outcomes and is unclear/unknown for the motor skills outcome measure (TOMI) as identity and blinding of outcome assessors not reported, and high risk for all core autism features outcomes (assessed with the DIPAB) as although investigator blinded to group assignment, outcome measure based on parental interview and parents were non-blind to group assignment and other potentially confounding factors 5. Risk of selective reporting bias is unclear/unknown as trial protocol is not registered on ClinicalTrials.gov or ISRCTN
Notes	Data could not be extracted for IQ or speech and language outcomes as N<10/arm for analysis due to missing data

1.7.11 KOUIJZER2010

Study ID	KOUIJZER2010
Bibliographic reference	Kouijzer MEJ, van Schie HT, de Moor JMH, Gerrits BJL, Buitelaar JK. Neurofeedback treatment in autism. preliminary findings in behavioral, cognitive, and neurophysiological functioning. Research in Autism Spectrum Disorders. 2010;4:386-399.
Methods	**Allocation:** Randomised **Matching:** No matching **Blindness:** Non-blind **Setting:** Educational (specialist) **Raters:** Parent- and teacher-rated **Country:** Netherlands
Participants	**Diagnosis:** DSM-IV ASD (40% Autism, 40% PDD-NOS, 20% Asperger's disorder) **Coexisting conditions:** None reported **Qualifying Diagnostic Assessment:** Diagnosis corroborated by an independent child psychiatrist through studying participant files **N:** 20 **Age:** Range not reported but inclusion criteria 8-12 years (mean: 9.3 years) **Sex:** 15% female **Ethnicity:** Not reported **IQ:** Not reported (but inclusion criteria IQ=>80) **Inclusion criteria:** Children were included if they: attended one of two special education schools; were aged 8-12 years; had an IQ=>80; had a previous DSM-IV diagnosis of ASD (made by certified child psychiatrist or health care psychologist) and corroborated by an independent child psychiatrist through studying participant files **Exclusion criteria:** Children were excluded if they: were using medication; had a history of severe brain injury; had a coexisting condition such as ADHD or epilepsy
Interventions	**Experimental Intervention: Neurofeedback.** Intervention involves recording participants' electroencephalographic (EEG) activity, showing them their oscillatory brain activity as it is recorded (using bar graphs to reflect the amplitude of a particular frequency) and training the participant to 'move up or down' their brain activity while observing the amplitude of their own brain waves. The targeted oscillatory activity was to reduce theta activity over frontal and central electrodes. Neurofeedback treatment protocols were individualized based on their EEG activity and the Neuroguide database (Thatcher et al., 2003) and included a number of electrode locations over frontal or central scalp (N=5 Cz; N=2 Fz; N=3 F4) and varying theta frequency bands (N=3 3-7Hz; N=2 3-8 Hz; N=1 3-6Hz; N=1 4-7Hz; N=1 4-8Hz; N=1 5-7Hz; N=1 5-8Hz) **Delivery of intervention:** Intervention administrator not reported **Format or method of administration:** Individual **Intensity:** Actual intensity not reported but planned intensity was an estimated 18.7 hours (40 sessions; 0.9 hour/week) **Duration of intervention:** 20 weeks **Total duration of follow-up:** 46 weeks (but data cannot be extracted for 6-month post-intervention follow-up)

Outcomes	**Direct outcome:** **Core autism feature: Overall autistic behaviours** (as measured by parent- and teacher-rated Social Communication Questionnaire [SCQ] - Total score) **Indirect outcomes:** **Core autism features: Impaired reciprocal social communication and interaction** (as measured by parent- and teacher-rated Social Responsiveness Scale [SRS] - Total score and Social Awareness, Social Cognition, Social Communication, Social Motivation, and Autistic Mannerisms subscales; parent- and teacher-rated SCQ - Reciprocal social interactions and Communication subscales; and the parent- and teacher-rated Children's Communication Checklist [CCC-2] - Total score and Social relations, Interests, Inappropriate initialization, Stereotyped conversation, Context use, Non-verbal communication, and Pragmatics subscales); **Restricted interests and rigid and repetitive behaviours** (as measured by parent- and teacher-rated SCQ - Stereotyped behaviour subscale) **Coexisting problem or disorder: Speech and language** (as measured by the parent- and teacher-rated CCC-2 Speech production, Syntax, Semantics, and Coherence subscales)
Study Design	RCT
Source of funding	Not reported
Limitations	1. Risk of selection bias is unclear/unknown as randomisation method is unclear, insufficient detail reported with regards to allocation concealment, and the groups were not comparable at baseline (group difference in diagnoses - in the experimental group 60% had autism and 40% had PDD-NOS and no participants had Asperger's disorder and in the control group 20% had autism, 40% had PSS-NOS and 40% had Asperger's disorder) 2. High risk of performance bias as intervention administrators were non-blind 3. High risk of response bias as participants were non-blind 4. High risk of detection bias as outcome assessors (parents and teachers) were non-blind 5. High risk of selective reporting bias as data cannot be extracted for the 6-month post-intervention follow-up 6. High risk of other bias due to potential conflict of interest as neurofeedback equipment provided by the manufacturer
Notes	Not applicable

1.7.12 MOLLOY2002

Study ID	MOLLOY2002
Bibliographic reference	Molloy CA, Manning-Courtney P, Swayne S, Bean J, Brown JM, Murray DS, et al. Lack of benefit of intravenous synthetic human secretin in the treatment of autism. Journal of Autism and Developmental Disorders. 2002;32:545-551.
Methods	**Allocation:** Randomised **Matching:** No matching reported **Blindness:** Participants, parents and outcome assessors were all blind to treatment allocation. Care administrators were not blind, but had no involvement in outcome measures **Setting:** Not reported **Raters:** Clinical psychologist and two speech and language pathologists **Country:** USA
Participants	**Diagnosis:** DSM-IV diagnosis of autism **Coexisting conditions:** No details on coexsisting conditions reported **Qualifying Diagnostic Assessment:** Multidisciplinary evaluation (no further information reported). Children who had not received the multidisciplinary evaluation were accepted into the study if they had a diagnosis from a developmental pediatrician. **N:** 42 **Age:** Range: not reported (mean: 6.2 years) **Sex:** 12% female **Ethnicity:** 76% white **IQ:** Not reported **Inclusion criteria:** Children were included if they: were aged 2-15 years old; had a DSM-IV diagnosis of autism based on a multidisiplinary evaluation or had a diagnosis from a developmental pediatrician **Exclusion criteria:** Children were excluded if: they had previously received secretin; it was deemed unsafe to paarticipate in the study due to other medical conditions; they had been diagnosed with other genetic or chromosomal disorders; neuroimaging revealed a strutural 'abnormaility'; they had acute or chronic pancreatic disease
Interventions	**Experimental Intervention: Synthetic human secretin** (ChiRhoClin, Inc., Silver Spring, MD). The vials for the treatment group contained 16 µg synthetic human secretin, 1.5 mg cysteine hydrochloride, 20 mg mannitol and 8 ml normal saline. **Control Intervention: Saline placebo** **Delivery of intervention:** The intervention was delivered to children individually by a research pharmacist **Format or method of administration:** Vials containing synthetic human secretin **Intensity:** 2 IU/kg **Duration of intervention:** Single dose **Total duration of follow-up:** 12 weeks (including cross-over period but data were extracted only for 6 week period corresponding to the end of the first phase)
Outcomes	**Direct Outcome** **Core autism feature: Overall autistic behaviours** (as measured by Childhood Autism Rating Scale [CARS] - Total score; Gilliam Autism Rating Scale [GARS]

	- Autism Quotient) **Indirect Outcomes** **Coexisting problems or disorders: Speech and language** (as measured by Mullen Scale of Early Learning [MSEL] - Receptive language subscale; Peabody Picture Vocabulary Test-3 [PPVT]; mean length of utterance and type-token ratio measured using behavioural observation); **IQ** (as measured using the Merrill-Palmer scale)
Study Design	RCT (crossover)
Source of funding	Grant # 4 T73 MC 00032-10 awarded by the Maternal and Child Health Bureau, Health Resources and Service Administration, DHHS and by Grant # M01 RR-08084, NIH.
Limitations	1. Unclear risk of selection bias: methods of randomisation and concealment of allocation not reported 2. High risk of selective reporting: the study is not registered and not all outcomes are reported within the study with no data reported for the Aberrant Behaviour Checklist or the Autism Behaviour Checklist
Notes	The number of drop outs from the study is unclear. The paper reports that 68 participants were randomly selected to participate in the study; 6 of these participants had previously had secretin treatment and 2 participants did not meet the criteria for autism. Due to some families seeking secretin from other sources, making them in eligible for the study and some families changing their minds about involvement in the study, 42 participants completed treatment, but it is not clear whether these participants had been assigned to groups or whether any received secretin before leaving the study. Some participants were given a later start date, but interim analysis showed that treatment differences were not strong enough to continue with the study. Demographic information and outcome measures are based on 42 participants.

1.7.13 OWLEY1999/2001

Study ID	OWLEY1999/2001
Bibliographic reference	Owley T, Steele E, Corsello C, Risi S, McKaig K, Lord C, et al. A double-blind, placebo-controlled trial of secretin for the treatment of autistic disorder. Medscape General Medicine. 1999;1(3). Available from: http://www.medscape.com/viewarticle/715516. Owley T, McMahon W, Cook EH, Laulhere T, South M, Mays LZ, et al. Multisite, double-blind, placebo-controlled trial of porcine secretin in autism. Journal of the American Academy of Child and Adolescent Psychiatry. 2001;40:1293-1299.
Methods	**Allocation:** Randomised **Matching:** No matching reported **Blindness:** Particpants, parents and all outcome assessors were blind to treatment allocation **Setting:** Not reported **Raters:** Parents and other unreported outcome assessors **Country:** USA
Participants	**Diagnosis:** DSM-IV Autistic Disorder **Coexisting conditions:** Coexisting conditions not reported **Qualifying Diagnostic Assessment:** Autism Diagnostic Interview-Revised (ADI-R) and Autism Diagnostic Observation Schedule-Generic (ADOS-G) **N:** 56 **Age:** Range: 2.9-10.4 years (Mean: 6.7 years) **Sex:** 14% female **Ethnicity:** 80% white **IQ:** Full scale IQ not reported. Mean NVIQ 56.4 (based on the Differential Abilities Scale or the Mullen Scales of Early Learning) **Inclusion criteria:** Children were included if they: had a DSM-IV diagnosis of Autistic Disorder based on the Autism Diagnostic Interview-Revised, the Autism Diagnostic Schedule-Generic and the clinical judgement of a child psychologist, psychiatrist or pediatric neurologist; had a non-verbal score of >35 based on the Differential Abilities Scale or a score of >30 on the Mullen Scales of Early Learning; had an overall age equivalents on the Vineland Adaptive Behaviour Scale of $\geq$24 months. **Exclusion criteria:** Children were excluded if: they had an alergy to porcine products; there was not agreement between all three of the diagnostic measures on the diagnosis of Autistic Disorder; there was a change in the dosage of their medication in the 8 weeks preceding the start of the study; excluding autism, they had a significant history of medical illness including nonfebrile seizures.
Interventions	**Experimental Intervention: Porcine secretin** (Ferring Pharmaceuticals, Tarrytown, NY) **Control Intervention: Saline placebo** **Delivery of intervention:** Children received the intervention individually. Details on care administrators were not reported **Format or method of administration:** Intravenous **Intensity:** 2 CU/kg **Duration of intervention:** Single dose

	Total duration of follow-up: 8 weeks (including cross-over period but data were extracted only for 4 week period corresponding to the end of the first phase)
Outcomes	**Direct Outcome** **Core autism feature: Impaired reciprocal social communication and interaction** (as measured by Autism Diagnostic Observation Schedule [ADOS] - Social interaction, Communication, and Communication + Social interaction subscales; and Gilliam Autism Rating Scales [GARS] - Communication and Social interaction subscales) **Indirect Outcome** **Core autism feature: Overall autistic behaviours** (as measured by GARS - Autism quotient; Clinical Global Impression [CGI] scale); **Repetitive behaviours and rigid and restrictive interests** (as measured by the ADOS - Stereotyped behaviors/interests subscale; and GARS - Stereotyped behaviour subscale) **Behaviour that challenges** (as measured by the Aberrant Behaviour Scale [ABC] - Irritability, Lethargy, Stereotypy, Hyperactivity, and Inappropriate speech subscales) **Coexisting problems or disorders: Adaptive behaviour** (as measured by Vineland Adaptive Behaviour Scale [VABS] - Adaptive behaviour composite, and Daily living skills, Communication, and Socialization subscales); **Speech and language** (as measured by Mullen Scales of Early Learning [MSEL] or the Peabody Picture Vocabulary Test-III [PPVT] - Receptive language [age in months]); **Fine and gross motor skills** (as measured by the MSEL or the Developmental Test of Visual Perception, 2nd ed. [DTVP-2] - Fine motor [age in months])
Study Design	RCT (crossover)
Source of funding	University of California at Davis Medical Investigation of Neurodevelopmental Disorders Institute, grants from the NIMH, the Jean Young and Walden W. Shaw Foundation, and the Irving B. Harris Foundation.
Limitations	1. Unclear risk of selection bias: the study reports that the randomisation was carried out by the investigational pharmacy at each site. No further details on randomisation reported. 2. Unclear risk of selective reporting: all outcomes are reported but the study has not been registered
Notes	Not applicable

1.7.14 SAMPANTHAVIVAT2012

Study ID	SAMPANTHAVIVAT2012
Bibliographic reference	Sampanthavivat M, Singkhwa W, Chaiyakul T, Karoonyawanich S, Ajpru H. Hyperbaric oxygen in the treatment of childhood autism: a randomised controlled trial. Diving and Hyperbaric Medicine. 2012;42:128-133.
Methods	**Allocation:** Randomised **Matching:** No matching reported **Blindness:** Investigators, participants, carers and outcome assessors were blinded. **Setting:** Not reported

	Raters: Parent- and clinician-rated **Country:** Thailand
Participants	**Diagnosis:** DSM-IV-TR Autism **Coexisting conditions:** None reported **Qualifying Diagnostic Assessment:** Not reported **N:** 60 (N=60 randomised but demographic and outcome data only reported for completers N=58) **Age:** Range not reported but inclusion criteria 3-9 years (mean: 5.9 years) **Sex:** 17% female **Ethnicity:** Not reported **IQ:** Not reported **Inclusion criteria:** Children were included if they: met the criteria for autism based on the DSM-IV-TR; had never received HBOT; were 3-9 years old. **Exclusion criteria:** Children were excluded if: they had a seizure disorder; current ear infections; current respiratory tract infections; had current or recent chemotherapy; suffered from uncontrolled asthma; suffered from severe claustrophobia; received ongoing chelation treatment; had a history of spontaneous pneumothorax
Interventions	**Experimental Intervention: Hyperbaric Oxygen Therapy (HBOT)** at 153 kPa (1.5 ATA) with 100% oxygen was delivered to participants through a multiplace chamber. **Control Intervention: Sham HBOT** was delivered to participants with air pressured at 116 kPa (1.15 ATA) **Delivery of intervention:** Intervention administrators were hyperbaric technicians **Format or method of administration:** Individual **Intensity:** Children received 5 hour-long sessions a week for 20 sessions. A total of 20 hours (5 hours per week). **Duration of intervention:** 4 weeks **Total duration of follow-up:** 4 weeks
Outcomes	**Direct outcome:** **Core autism feature: Overall autistic behaviours** (as measured by the parent- and clinician-rated Autism Treatment Evaluation Checklist [ATEC] - Total, and Speech/Language/Communication, Sociability, Sensory/Cognitive Awareness, and Health/Physical/Behavior subscales; and parent- and clinician-rated Clinical Global Impression Scale: Severity [CGI-S] and Clinical Global Impression-Improvement [CGI-I]) **Indirect outcome:** **Adverse events** (as measured by number of participants who experienced minor-grade ear barotrauma events during the trial)
Study Design	RCT
Source of funding	HM Queen Sirikit Naval Hospital, Royal Thai Navy Foundation
Limitations	1. High risk of performance bias as intervention administrators were non-blind 2. Risk of detection bias unclear/unknown for adverse event outcome as unclear if 4 weeks sufficient follow-up duration to detect potential longer-term adverse events and unclear what outcome measure was used and identity and blinding of outcome assessor not reported 3. Risk of selective reporting bias is unclear/unknown as trail protocol is not registered on ClinicalTrials.gov or ISCRCTN

Notes	Blinding tested using parental survey and post-intervention parental beliefs about treatment allocation were 69% of those in the HBOT group believed they were in active intervention condition relative to 83% of those in sham HBOT group. This difference was statistically significant ($p<0.001$) and indicates that blinding was successful.

1.7.15 SANDLER1999

Study ID	SANDLER1999
Bibliographic reference	Sandler AD, Sutton KA, DeWeese J, Girardi A, Sheppard V, Bodfish JW. Lack of benefit of a single dose of synthetic human secretin in the treatment of autism and pervasive developmental disorder. New England Journal of Medicine. 1999;341:1801-1806.
Methods	**Allocation:** Randomised **Matching:** No matching reported by children were stratified based on a 'median split' according to the median age **Blindness:** Participants, parents and outcome assessors were blind to treatment allocation. Unclear if care administrators were blind. **Setting:** Not reported **Raters:** Parents and teachers **Country:** USA
Participants	**Diagnosis:** DSM-IV diagnosis of Autism or Pervasive Developmental Disorder not otherwise specified. Diagnosis: 67% autism; 33% PDD-NOS. **Coexisting conditions:** Details of coexisting conditions not reported **Qualifying Diagnostic Assessment:** Childhood Autism Rating Scale or Autism Behaviour Checklist **N:** 60 **Age:** Range: not reported (Mean: 7.5 years) **Sex:** Not reported **Ethnicity:** Not reported **IQ:** Range not reported (mean: 62.2). Test not reported **Inclusion criteria:** Children were included if they: had written consent from their parents; were aged between 3 and 14; had not previously had secretin; a previous diagnosis of autism; no history of pancreatitis, gastrinomal or inflammatory bowel disease. **Exclusion criteria:** Not reported
Interventions	**Experimental Intervention: Synthetic human secretin.** The vials contained a sterile, lyophilised powder made of 16 µg of synthetic human secretin, 1.5 mg of cysteine hydrochloride, 20 mg of mannitol, and 8ml saline. **Control Intervention: Saline placebo** **Delivery of intervention:** The intervention was delivered to children individually. Care administrators not reported (but administered using double-blind procedure) **Format or method of administration:** Intravenous (delivered with identical-appearing syringe) **Intensity:** 0.4 µg/kg **Duration of intervention:** Single dose **Total duration of follow-up:** 4 weeks (including 3-week post-intervention follow-up)
Outcomes	**Direct Outcome** **Core autism feature: Overall autistic behaviours** (as measured by Autism Behaviour Checklist [ABC] - Total score, and Sensory function, Social relatedness, Body and object use, Language, and Socialization subscales; Clinical Global Impression [CGI] scale - Response to social interaction, Social initiation, Use of speech, Types of repetitive behaviour, Behaviour problems, Activity level, Sleep problems, and Digestive problems subscales)

	Indirect Outcome **Coexisting problem or disorder: Adaptive behaviour** (as measured by the parent-rated or teacher-rated Vineland Adaptive Behavior Scale [VABS] - Communication subscale)
Study Design	RCT
Source of funding	Supported by the Thoms Health Services Foundation and by a Public Health Service grant (30615) from the National Institutes of Child Health and Human Development.
Limitations	1. Unclear risk of selection bias: method of randomisation and concealment of allocation not reported 2. High risk of selective reporting: the study is not registered and data could not be extracted for the Treatment Emergent Symptoms Scale
Notes	If participants met the inclusion criteria, they were screened for autism using the a cut-off score of >30 on the Childhood Autism Rating Scale or >60 on the Autism Behaviour Checklist. Children who had severe social or communication impairments or displayed repetitive behaviour, but did not meet the DSM-IV criteria of autism were given a diagnosis of Pervasive Developmental Disorder not otherwise specified. All outcomes are based on change scores. The author was contact for endpoint scores but no response received

1.7.16 UNIS2002

Study ID	UNIS2002
Bibliographic reference	Unis AS, Munson JA, Rogers SJ, Goldson E, Osterling J, Gabriels R, et al. A randomized, double-blind, placebo-controlled trial of porcine versus synthetic secretin for reducing symptoms of autism. Journal of the American Academy of Child and Adolescent Psychiatry. 2002;41:1315-1321.
Methods	**Allocation:** Randomised **Matching:** Yes, participants were matched by age and Vineland communication standard score prior to randomisation **Blindness:** Participants, parents, teachers and outcome assessors were blind to treatment allocation. Blinding of care administrators not reported **Setting:** Academic **Raters:** Teachers, parents and unspecified outcome assessors **Country:** USA
Participants	**Diagnosis:** DSM-IV autism or pervasive developmental disorder not otherwise specified **Coexisting conditions:** Details of coexisting conditions not reported **Qualifying Diagnostic Assessment:** Autism Diagnostic Observation Schedule (ADOS) **N:** 90 children were randomised to groups; 85 children completed study and all outcome measures and demographic information based on 85 participants **Age:** Range: not reported (Mean: 6.5 years) **Sex:** Not reported **Ethnicity:** Not reported **IQ:** Not reported **Inclusion criteria:** Children were included if they: were aged 3-12 years; had a DSM-IV diagnosis of autism or PDD-NOS from a clinical psychologist or physician, which investigators were able to confirm with the Autism Diagnostic Observation Schedule (ADOS); had a non-verbal IQ score, from within three years of the study, of ≥35 **Exclusion criteria:** Children were excluded if they: had any comorbid conditions linked to autism (e.g. tuberous sclerosis, fragile X); had a diagnosis of epilepsy; had previously received secretin; were allergic to pork products; had been taking psychotropic medication in the six months preceding the study.
Interventions	**Experimental Intervention: Secretin** (two active arms: Porcine secretin and Synthetic porcine secretin). **Delivery of intervention:** Children received the intervention individually. Care administrators not reported (but Infusions were administered in a hospital where the child was not known) **Format or method of administration:** Intravenous **Intensity:** 2 CU/kg of porcine secretin or 0.4 µg/kg of synthetic porcine secretin **Duration of intervention:** Single dose **Total duration of follow-up:** 4 weeks
Outcomes	**Direct Outcome** **Core autism feature: Impaired reciprocal social communication and interaction** (as measured by Autism Diagnostic Observation Schedule [ADOS]-Commuication and Social interaction subscales;change scores)

	Indirect Outcome **Core autism feature: Overall autistic behaviours** (as measured by the parent-rated or teacher-rated Secretin Outcome Survey [SOS] - Total score, and Social, Communication, Repetitive behaviour, Digestive, Mood, Sensory, Hyperactivity, Lethargy, and Sleep subscales; change scores) **Behaviour that challenges** (as measured by the parent-rated or teacher-rated Aberrant Behaviour Checklist [ABC] - Total, and Irritability, Lethargy, Stereotypy, Hyperactivity, and Inapprorpriate speech subscales; change scores) **Coexsiting problems or disorders: Speech and language** (as measured by Expressive One Word Picture Vocabulary Test-Revised [EOWPVT-R]; MacArthur Communication Developmental Inventories [CDI]: Vocabulary)
Study Design	RCT
Source of funding	Grant from the NICHD and the NIDCD (PO1HD34565). Grant from the NICHD (PO1HD35468). ADD grant 90dd041401 and MCH grant MCJ08941301. Grant from the NCRR (MO1-RR00069).
Limitations	1. Unclear risk of selection bias: Methods of randomisation and concealment of allocation not reported 2. Unknown risk of attrition bias: The study reports that five participants dropped out of the study, but no details reported on which treatment groups drop-outs were in
Notes	For data analysis initial comparisons tested for significant differences between the two active arms (porcine secretin and synthetic porcine secretin), where there were no significant differences these two groups were combined for meta-analysis, where there was a significant difference between these two treatment arms the two interventions were entered into meta-analysis as subgroups (but with the subtotal function disabled). Contacted author regarding endpoint rather than change score data but no reply to request so change scores entered into meta-analyses.

1.7.17WHITELEY2010

Study ID	WHITELEY2010
Bibliographic reference	Whiteley P, Haracopos D, Knivsberg A-M, Reichelt KL, Parlar S, Jacobsen J, et al. The ScanBrit randomised, controlled, single-blind study of a gluten- and casein-free dietary intervention for children with autism spectrum disorders. Nutritional Neuroscience. 2010;13:87-100.
Methods	**Allocation:** Randomised **Matching:** Stratified for age and Vineland Adaptive Behavior (VABS) composite scores **Blindness:** Investigator (who was also outcome assessor blinded) but parents and participants non-blind **Setting:** Home **Raters:** Investigator- and parent-rated **Country:** Denmark
Participants	**Diagnosis:** ICD-10 ASD (69% autism, 31% ASD) **Coexisting conditions:** None reported **Qualifying Diagnostic Assessment:** Prior ICD-10 diagnosis of autism made by the Center for Autisme (based on previously completed ADOS and ADI-R) or other child psychiatric clinics (no corroboration of diagnosis for current study) **N:** 72 **Age:** Range not reported but inclusion criteria 4-11 years (mean: 8.2 years) **Sex:** 11% female **Ethnicity:** Not reported **IQ:** Not reported **Inclusion criteria:** Children were included if they: were aged 4-10.9 years; had a formal ICD-10 diagnosis of autism made by the Center for Autisme (based on previously completed ADOS and ADI-R) or other child psychiatric clinics (no corroboration of diagnosis for current study); had an abnormal urinary peptide profile (based on blind independent double-assessment) **Exclusion criteria:** Children were excluded if they had: a diagnosis of epilepsy, fragile-X syndrome, tuberous sclerosis; a developmental age under 24 months. Childrens' data was excluded from analysis if they were concurrently taking any psychotropic medication
Interventions	**Experimental Intervention: Gluten-free and casein-free diet.** A strict gluten-free and casein-free diet was introduced over the course of 2 weeks. Nutritionists monitored the experimental group for the trial duration to ensure dietary compliance and nutritional intake. The experimental group were also advised to take a mult-vitamin supplement including calcium for the trial duration to compensate for any nutritional deficiency during the intervention **Control Intervention: Treatment-as-usual.** Control participants were instructed to continue with their current diet **Delivery of intervention:** Parents delivered the intervention **Format or method of administration:** Parent training **Intensity:** Unknown (compliance not recorded) **Duration of intervention:** Data extracted for 8-month intervention as after this point duration was variable across participants **Total duration of follow-up:** 24 months (experimental group received diet and control group received treatment-as-usual for 8 months, at 8 months

	interim assessment of change in scores for the experimental group on one of several measures [ADOS, GARS, VABS, ADHD-IV] against pre-defined statistical thresholds as evidence of improvement, if threshold exceeded both groups allocated to receive diet and re-assessed at 20 months, if threshold not exceeded experimental and control group continued to receive their respective interventions and then re-assessed at 12 months, if experimental group exceeded threshold at 12 months both groups received diet intervention and re-assessed at 24 months, if threshold not exceed then both groups stopped trial)
Outcomes	**Direct outcome:** **Core autism feature: Impaired reciprocal social communication and interaction** (as measured by Autism Diagnostic Observation Schedule [ADOS] - Communication [change score] and Social Interaction [change score] subscales; Gilliam Autism Rating Scale [GARS] - Social Interaction [change score] and Communication [change score]) **Indirect outcome:** **Core autism feature: Restricted interests and rigid and repetitive behaviours** (as measured by ADOS - Repetitive Behaviours [change score] subscale; and GARS - Stereotyped behaviour [change score] subscale) **Coexisting problems or disorders: Adaptive behaviour** (as measured by Vineland Adaptive Behaviour Scale [VABS] - Communication [change score], Socialization [change score], and Daily Living Skills [change score] subscales); **ADHD symptoms** (as measured by Attention-Deficit Hyperactivity Disorder-IV rating scale based on DSM-IV criteria [ADHD-IV] - Inattention [change score], and Hyperactivity [change score] subscales) **Adverse events** (as measured by dichotomous measure of any adverse event)
Study Design	RCT
Source of funding	Center for Autisme, the Nils O. Seim Family Fund for Medical Research, the Eric Birger Christensen Fond, the Norwegian Protein Intolerance Association and the Robert Luff Foundation
Limitations	1. Risk of selection bias is unclear/unknown as randomisation method is unclear and group comparability at baseline unclear 2. High risk of performance bias as intervention administrators were non-blind parents 3. High risk of response bias as participants were non-blind 4. Risk of detection bias is different for different outcomes: Unclear/unknown for the GARS as the identity and blinding of outcome assessors not reported and for the adverse event measure as adverse events monitored by study nutritionist who was non-blind and outcome measure for recording adverse events not reported so reliability and validity unclear; High risk for the VABS and the ADHD-IV as parent-reported and non-blind to treatment allocation and other potentially confounding factors 5. High risk of attrition bias as over twice as many dropouts in the experimental group relative to the controls (32% in experimental group and 15% in the control group) 6. High risk of other bias due to potential conflict of interest as two investigators are members of the Norwegian Protein Intolerance Association, which also partially funded the study and two investigators undertook commercial analysis of urine samples from people with ASD and related conditions whilst involved in the study.

Notes	Trial protocol is registered on ClinicalTrials.gov, Study ID NCT00614198. Data cannot be extracted from paper but results on ClinicalTrials.gov, standard errors reported on ClinicalTrials.gov were converted to standard deviations for meta-analysis. Contacted author requesting endpoint rather than change scores but no reply.

1.7.18WONG2002/CHEUK2011

Study ID	WONG2002/CHEUK2011
Bibliographic reference	Wong V, Sun JG. Research on tongue acupuncture in children with autism. The 9th International Child Neurology Congress and the 7th Asian and Oceanian Congress of Child Neurology; 2002. Cheuk DKL, Wong V, Chen WX. Acupuncture for autism spectrum disorders (ASD)(Review). The Cochrane Database of Systematic Reviews. 2011;9:Art. No CD007849. Available from: DOI: 10.1002/14651858.CD007849.pub2.
Methods	**Allocation:** Randomised **Matching:** No matching reported **Blindness:** Outcome assessors were blind, but participants and care administrators were not blind **Setting:** Not reported **Raters:** Blinded assessors, but parents were involved in some outcome assessments. Parents were not blind. **Country:** Not reported
Participants	**Diagnosis:** DSM-IV Autism Spectrum Disorder **Coexisting conditions:** Not reported **Qualifying Diagnostic Assessment:** Autism Diagnostic Interview-Revised (ADI-R) **N:** 30 **Age:** Range: not reported (Mean: 7.17 years) **Sex:** 3% female **Ethnicity:** Not reported **IQ:** Not reported **Inclusion criteria:** Children were included if they: were aged 3-15 years; had a confirmed DSM-IV diagnosis of ASD based on the Autism Diagnostic Interview-Revised (ADI-R); had a score of >30 on the Childhood Autism Rating Scale (CARS) **Exclusion criteria:** Children were excluded if: they had epilepsy, fragile X syndrome, tuberous sclerosis or any other associated neurological disorders
Interventions	**Experimental Intervention: Acupuncture** was delivered with Hwato needles to five acupoints on the tongue. The acupuncture sessions lasted for <15 seconds and parents were present throughout. Information on educational programme not reported. **Delivery of intervention:** Acupuncture was delivered individually by a qualified acupuncturist. Educational programme unclear. **Format or method of administration:** Individual **Intensity:** 15 seconds of acupuncture daily, five days a week for 8 weeks (40 sessions). A total of 10 minutes (1.25 minutes a week) **Duration of intervention:** 8 weeks **Total duration of follow-up:** 8 weeks
Outcomes	**Direct Outcome** **Core autism feature: Overall autistic behaviours** (as measured by Ritvo-Freeman Real-life Rating Scale [RLRS] - Total score and Motor, Social, Affective, Sensory, and Language subscales; and Clinical Global Impression [CGI] Scale - Response to social interaction, Social initiation, Use of speech, Repetitive behaviour, Behaviour problem, Activity level, Sleep problem, and

	Digestive problem subscales) **Indirect Outcome** **Coexisting problem or disorder: Adaptive behaviour** (as measured by Functional Independence Measure for Children [WeeFIM] - Total score, and self-care, mobility, and cognition subscales)
Study Design	RCT
Source of funding	Not reported
Limitations	1. High risk of performance bias: participants and care administrators are not blind to treatment allocation and potential care confounds as the conventional education programme differed for each participant which may introduce bias 2. Unclear risk of detection bias on all measures: All outcomes were measured by blinded assessors, but some outcomes involved input from parents who were not blind to treatment allocation or confounding variables and systematic review from which data was extracted does not report which outcome measures relied on non-blind parental report 3. High risk of selective reporting: the study has not been registered and some outcomes reported with insufficient detail to be entered into meta-analysis (side effects narratively reported but not in sufficient detail to enter into meta-analysis)
Notes	The original paper was excluded from the analysis on that basis that it was a conference paper. The study was then included in a systematic review and all information reported here is from that source (note that change scores rather than endpoint scores included in the original systematic review and extracted here)

1.7.19WONG2008/CHEUK2011

Study ID	WONG2008/CHEUK2011
Bibliographic reference	Wong CL. Acupuncture and autism spectrum disorders - an assessor-blinded randomised controlled trial (M Phil). Hong Kong: University of Hong Kong; 2008. Cheuk DKL, Wong V, Chen WX. Acupuncture for autism spectrum disorders (ASD)(Review). The Cochrane Database of Systematic Reviews. 2011;9:Art. No CD007849. Available from: DOI: 10.1002/14651858.CD007849.pub2.
Methods	**Allocation:** Randomised **Matching:** Children were matched by age and severity of autism (according to Childhood Autism Rating Scale [CARS] score) **Blindness:** Participants and individuals administering care were non blind. Outcome assessors were blind. **Setting:** Not reported **Raters:** Blinded outcome assessors (no further information reported). Parents (non-blind) were involved in some measures. **Country:** Not reported
Participants	**Diagnosis:** DSM-IV diagnosis of Autism Spectrum Disorder **Coexisting conditions:** Not reported, but children were excluded if they had other neurological, psychaitric or genetic disorders **Qualifying Diagnostic Assessment:** Autism Diagnostic Interview-Revised (ADI-R) and Autism Diagnostic Observation Schedule (ADOS) **N:** Unclear how many were assigned to groups; 36 participants are included in analysis. However, the systematic review reports there were drop-outs and it is not clear whether available case or last observation carried forward analysis was used. **Age:** 7.51 **Sex:** 6% female **Ethnicity:** Not reported **IQ:** Not reported **Inclusion criteria:** Children were included if they: had a DSM-IV diagnosis of ASD based on the Autism Diagnostic Interview-Revised (ADI-R) and the Autism Diagnostic Observation Schedule; were aged 3-12 years **Exclusion criteria:** Children were excluded if they: had epilepsy that was being treated by antiepileptic drugs; had other neurological, psychiatric or genetic disorders; had received acupuncture in the year prior to starting the intervention; had parents who did not complete all assessments
Interventions	**Experimental Intervention: Acupuncture** was delivered with Hwato needles to five acupoints, with the "De Qi" sensation being elicited as far as possible. Electrical stimulation was applied with the Hwato SDZ electronic system. Different stimulation was given to those with different syndromes, based on Chinese medicine; deficiency syndrome (25Hz), deficiency-excess complex (50Hz), excess syndrome (75Hz). Sessions lasted 30 minutes. Both groups received a conventional education programme (no further details reported). **Delivery of intervention:** The intervention was delivered to children individually but a qualified acupuncturist. **Format or method of administration:** Individual **Intensity:** Children received acupuncture in 30 minutes sessions, 3 times a

	week for 8 weeks. A total of 24 sessions, equalling 12 hours (1.5 hours per week). **Duration of intervention:** 8 weeks **Total duration of follow-up:** 8 weeks
Outcomes	**Direct Outcome** **Core autism feature: Overall autistic behaviours** (as measured by the Ritvo-Freeman Real Life Rating Scale [RLRS]-Total score and Motor, Social, Affective, Sensory, and Language subscales; Autism Evaluation Treatment Checklist [ATEC] - Total score and Communication and speech, Socialbility, Sensory and cognitive awareness, and Physical health and behaviour subscales; Clinical Global Impression [CGI] - Total score) **Indirect Outcome** **Core autism feature: Impaired reciprocal social communication and interaction** (as measured by Autism Diagnostic Observation Schedule [ADOS] -Communication, and Social interaction subscales) **Behaviour that challenges** (as measured by Aberrant Behaviour Checklist [ABC]-Total score, and Irritability, Lethargy, Stereotypy, Hyperactivity and Inappropriate speech subscales) **Coexisting problem or disorder: Adaptive behaviour** (as measured by the Functional Independence Measure for Children [WeeFIM] - Total score, and self-care, mobility, cognition, comprehension, expression, social interaction, problem solving, and memory subscales)
Study Design	RCT
Source of funding	Not reported
Limitations	1. Unclear risk of selection bias: randomisation done with a computer generated sequence but concealment of allocation not reported 2. High risk of performance bias: participants and care administrators are not blind to treatment allocation and potential care confounds as the conventional education programme differed for each participant which may introduce bias 3. Unclear risk of detection bias on all measures: All outcomes were measured by blinded assessors, but some outcomes involved input from parents who were not blind to treatment allocation or confounding variables and systematic review from which data was extracted does not report which outcome measures relied on non-blind parental report
Notes	The original paper was a dissertation and so was excluded on that basis. The study was then included in a systematic review and all information reported here is from that source (note that change scores rather than endpoint scores included in the original systematic review and extracted here)

1.8 CHARACTERISTICS OF EXCLUDED BIOMEDICAL INTERVENTION STUDIES

1.8.1 ALCANTARA2011

Reason for exclusion	Systematic review with no new useable data and any meta-analysis results not appropriate to extract

1.8.2 BARTHELEMY1981

Reason for exclusion	Data cannot be extracted due to cross-over design and unavailability of first phase data

1.8.3 BERTOGLIO2010

Reason for exclusion	Data cannot be extracted and authors replied to data request stating that unable to provide this data

1.8.4 CHAN2012

Reason for exclusion	Efficacy data cannot be extracted for outcomes of interest and authors did not respond to data request

1.8.5 CHEZ2000

Reason for exclusion	Non-randomised group assignment

1.8.6 CHRISTISON2006

Reason for exclusion	Systematic review with no new useable data and any meta-analysis results not appropriate to extract

1.8.7 COBEN2007

Reason for exclusion	Non-randomised group assignment

1.8.8 COPLAN2003

Reason for exclusion	Cross-over design and first phase data unavailable

1.8.9 DAVIS2012B

Reason for exclusion	Systematic review with no new useable data and any meta-analysis results not appropriate to extract

1.8.10 ESCH2004

Reason for exclusion	Systematic review with no new useable data and any meta-analysis results not appropriate to extract

1.8.11 GEIER2011

Reason for exclusion	Non-randomised group assignment (authors describe trial as randomised but placebo participants allocated first and all latter participants assigned to experimental group so not truly random)

1.8.12 GHANIZADEH2012

Reason for exclusion	Systematic review with no new useable data and any meta-analysis results not appropriate to extract

1.8.13 HANDEN2005

Reason for exclusion	Sample size was less than ten participants per arm (N<10/arm)

1.8.14 HOLTMANN2011

Reason for exclusion	Systematic review with no new useable data and any meta-analysis results not appropriate to extract

1.8.15 JARUSIEWICZ2002

Reason for exclusion	Efficacy data cannot be extracted and author did not respond to data request

1.8.16 KOUIJZER2009

Reason for exclusion	Sample size was less than ten participants per arm (N<10/arm)

1.8.17 KRISHNASWAMI2011

Reason for exclusion	Systematic review with no new useable data and any meta-analysis results not appropriate to extract

1.8.18 LEE2011

Reason for exclusion	Systematic review with no new useable data and any meta-analysis results not appropriate to extract

1.8.19 LEE2012

Reason for exclusion	Systematic review with no new useable data and any meta-analysis results not appropriate to extract

1.8.20 LELORD1981

Reason for exclusion	Non-randomised group assignment

1.8.21 LELORD1982

Reason for exclusion	Data cannot be extracted due to cross-over design and unavailability of first phase data

1.8.22 MARTINEAU1985

Reason for exclusion	Non-randomised group assignment

1.8.23 MCQUEEN2002

Reason for exclusion	Systematic review with no new useable data and any meta-analysis results not appropriate to extract

1.8.24 MILLWARD2008

Reason for exclusion	Systematic review with no new useable data and any meta-analysis results not appropriate to extract

1.8.25 MING2012

Reason for exclusion	Systematic review with no new useable data and any meta-analysis results not appropriate to extract

1.8.26 NAZNI2008

Reason for exclusion	Non-randomised group assignment

1.8.27 NETHERTON2011

Reason for exclusion	Systematic review with no new useable data and any meta-analysis results not appropriate to extract

1.8.28 NYE2005

Reason for exclusion	Systematic review with no new useable data and any meta-analysis results not appropriate to extract

1.8.29 PATEL2002

Reason for exclusion	Systematic review with no new useable data and any meta-analysis results not appropriate to extract

1.8.30 PETRUS2008

Reason for exclusion	Systematic review and no useable data could be extracted as sample sizes too small (N<10/arm)

1.8.31 PETRYK2004

Reason for exclusion	Systematic review with no new useable data and any meta-analysis results not appropriate to extract

1.8.32 PFEIFFER1995

Reason for exclusion	Systematic review with no new useable data and any meta-analysis results not appropriate to extract

1.8.33 ROBERTS2001

Reason for exclusion	Data cannot be extracted and no reply to data request sent to author

1.8.34 STURMEY2005

Reason for exclusion	Systematic review with no new useable data and any meta-analysis results not appropriate to extract

1.8.35 WANG2007/CHEUK2011

Reason for exclusion	Non-randomised group assignment (allocated according to the sequence of clinic attendence)

1.8.36 WHITELEY1999

Reason for exclusion	Non-randomised group assignment

1.8.37 WILLIAMS2005

Reason for exclusion	Systematic review with no new useable data and any meta-analysis results not appropriate to extract

1.8.38 WILLIAMS2012A

Reason for exclusion	Systematic review with no new useable data and any meta-analysis results not appropriate to extract

1.8.39 WILLIAMS2012B

Reason for exclusion	Systematic review with no new useable data and any meta-analysis results not appropriate to extract

1.8.40 WONG2007/CHEUK2011

Reason for exclusion	Sample size was less than 10 participants per arm (N<10/arm) for analysis due to dropout and the available case analysis method

1.8.41 YAN2007/CHEUK2011

Reason for exclusion	Non-randomised group assignment (allocated according to the sequence of clinic attendence)

1.8.42 ZHANG2012

Reason for exclusion	Non-randomised group assignment

1.9 REFERENCES OF EXCLUDED BIOMEDICAL INTERVENTION STUDIES

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