Early developmental intervention programs post hospital discharge to prevent motor and cognitive impairments in preterm infants (Review)

Spittle A, Orton J, Doyle LW, Boyd R

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Early developmental intervention programs post hospital discharge to prevent motor and cognitive impairments in preterm infants

Alicia Spittle¹, Jane Orton¹, Lex W Doyle², Roslyn Boyd³

¹Murdoch Children’s Research Institute, Royal Children’s Hospital, Parkville, Australia. ²Department of Obstetrics and Gynaecology, University of Melbourne, Melbourne, Australia. ³Murdoch Children’s Research Institute, Parkville, Australia

Contact address: Alicia Spittle, Murdoch Children’s Research Institute, Royal Children’s Hospital, 2nd Floor, Flemington Road, Parkville, Melbourne, 3052, Australia. alicia.spittle@rch.org.au.

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ABSTRACT

Background
Infants born preterm are at increased risk of developing cognitive and motor impairments compared with infants born at term. Early developmental interventions have been used in the clinical setting with the aim of improving the overall functional outcome for these infants. However, the benefit of these programs remains unclear.

Objectives
To review the effectiveness of early developmental intervention post-discharge from hospital for preterm (< 37 weeks) infants on motor or cognitive development.

Search methods
The Cochrane Neonatal Review group search strategy was used to identify randomised and quasi-randomised controlled trials of early developmental interventions post hospital discharge. Two review authors independently searched the Cochrane Central Register of Controlled Trials (CENTRAL, The Cochrane Library), MEDLINE Advanced, CINAHL, PsychINFO and EMBASE (1966 through February 2006).

Selection criteria
Studies included had to be randomised or quasi-randomised controlled trials of early developmental intervention programs that commenced within the first 12 months of life for infants born at < 37 weeks with no major congenital abnormalities. Intervention could commence as an inpatient; however, a post discharge component was necessary to be included in this review. The outcome measures were not pre-specified other than that they had to assess cognitive and/or motor ability. The rates of intellectual impairment, cerebral palsy and development co-ordination disorder were also documented.
Data collection and analysis

Data were extracted and entered by two independent review authors. Cognitive and motor outcomes were pooled in three age groups - infant (0 to 2 years), preschool (3 to < 5 years) or school age (5 to 17 years). Meta-analysis was carried out using RevMan 4.2 to determine the effects of early developmental intervention in the short (0 to 2 years), medium (3 to < 5 years) and long term (5 to 17 years). Subgroup analysis was carried out in relation to: gestational age, birthweight, brain injury, commencement of intervention, focus of intervention and study quality.

Main results

Sixteen studies met the inclusion criteria (2379 randomised patients). Six of these studies were RCTs and had strong methodological quality. There was variability with regard to the focus and intensity of the intervention, and in length of follow-up. Meta-analysis concluded that intervention improved cognitive outcomes at infant age (developmental quotient [DQ]; standard mean difference [SMD] 0.46 SD; 95% CI 0.36 0.57; P < 0.0001), and at preschool age (intelligence quotient [IQ]; SMD 0.46 SD; 95%CI 0.33, 0.59; P < 0.0001). However, this effect was not sustained at school age (IQ; SMD 0.02 SD; 95% CI -0.10, 0.14; P = 0.71). There was significant heterogeneity between studies for cognitive outcomes at infant and school ages. There was little evidence of an effect of early intervention on motor outcomes in the short, medium or long-term, but there were only two studies reporting outcomes beyond 2 years.

Authors’ conclusions

Early intervention programs for preterm infants have a positive influence on cognitive outcomes in the short to medium term. However, there was significant heterogeneity between the interventions included in this review. Further research is needed to determine which early developmental interventions are the most effective at improving cognitive and motor outcomes, and on the longer-term effects of these programs. Cost-effectiveness and access to services should also be evaluated since they are important factors when considering implementation of an early developmental intervention program for a preterm infant.

PLAIN LANGUAGE SUMMARY

Early developmental intervention programs post hospital discharge to prevent motor and cognitive impairments in preterm infants

Preterm infants (babies born before 37 weeks) are at risk of development problems, including problems with cognitive and motor development. Cognitive development refers to thinking and learning ability and motor development refers to the way infants move, such as sitting, crawling and walking. Early developmental interventions aim to reduce cognitive and/or motor problems; however, the benefits of these programs are not clear. A review of trials suggests early developmental intervention programs post discharge from hospital for preterm infants are effective at improving cognitive development in the short to medium term (up to preschool age). There is limited evidence that early developmental interventions improve motor outcome or long term cognitive outcome (up to school age). The early developmental intervention programs in this review had to commence within the first 12 months of life, focus on the parent-infant relationship and/or infant development and, although they could commence while the baby was still in hospital, they had to have a component that was delivered post-discharge from hospital. The early developmental intervention programs included in this review are different in content, frequency of intervention and focus of intervention. The variability in the intervention programs limits the conclusions that can be made about the effectiveness of early developmental interventions.

BACKGROUND

Infants born preterm or low birth weight are at increased risk of developing motor, cognitive and behavioural impairments compared with infants born at term (Doyle 2004; Pedersen 2000; Bhutta 2002). Despite improving rates of survival for extremely low birth weight infants over the past two decades, the rate of disabilities has remained relatively constant, with up to 50% of these infants...
later exhibiting developmental disabilities such as motor, cognitive or behavioural impairments (Bhutta 2002; Doyle 2004). Five to fifteen percent will have cerebral palsy (Tin 1997; VoHR 2005).

These neurosensory impairments are complex and often subtle, and may affect various aspects of the child’s development. At school age, children born preterm experience problems across most educational domains. They tend to have difficulties learning, particularly in applying mathematical concepts (Anderson 2003). Attentional problems and hyperactivity are commonly reported in children born prematurely (Horwood 1998). These can substantially affect academic achievement and social integration (Hoy 1992; Botting 1998; Sommerfelt 1996). Minor motor impairments, which are now classified as Developmental Coordination Disorder (DSM-IV), have also been found to be more prevalent in very low birth weight infants (Polatajko 1995; Holst 2002; Marlow 1989). These motor problems persist into adolescence and can affect school performance and self esteem (P咆s 1995). In adulthood, very low birthweight infants continue to exhibit higher rates of neurosensory impairments, with lower academic scores and a lower high school graduation rate compared with adults born at normal birth weights (Hack 2002).

The learning, behaviour and motor impairments in preterm children can be associated with medical risk factors [e.g. birth weight, gestational age, periventricular leukomalacia (PVL), intraventricular haemorrhage (IVH), respiratory distress syndrome and necrotising enterocolitis]; however, they account for only a portion of the variance associated with these long-term outcomes (VoHR 2000). Non-medical factors such as social class, parental education, parenting style, parental mental health, family structure, family functioning and the home environment are also associated with development. These factors are grouped into interventions that focus on the parent-infant relationship, the infant’s development, or both. While some interventions may specifically target motor or cognitive development, there is a strong relationship between these areas. For example, by influencing motor function, cognitive outcome may also be improved as it allows the infant more opportunity to interact with their environment (Thelen 1996; Becker 1999). The intervention may be seen as a prevention or treatment program. When intervention is begun at this early age in infants at high risk of neurodevelopmental problems, it is usually a prevention program. However, during the course of an intervention if a specific dysfunction becomes apparent this dysfunction would become the focus and be treated accordingly.

Primary Objectives

To determine the effect of early developmental intervention programs post hospital discharge on cognitive and motor development compared with standard medical follow-up of preterm infants at infant (0 - 2 years), preschool (3 - < 5 years) and school ages (5 - 17 years).
SECONDARY OBJECTIVES

To perform subgroup analysis to determine:

- the effect of gestational age, birthweight and brain injury (PVL/IVH) on cognitive and motor outcome in response to intervention compared with standard follow-up.
- the effect of interventions that commence as an inpatient compared with commencing post-hospital discharge compared with standard follow-up.

SUBGROUPS

Population subgroups:

- Gestational age: extremely preterm (< 28 weeks), very preterm (28 - < 32 weeks) or preterm (32 - < 37 weeks).
- Birth weight: extremely low birth weight (< 1000 g), very low birth weight (1000 - < 1500 g), low birth weight (1500 - < 2500 g).
- Brain injury: absence or presence of grade III or grade IV intraventricular haemorrhage and/or cystic periventricular leukomalacia or an abnormal ultrasound/ MRI diagnosed prior to the initiation of intervention.

Intervention subgroups:

- Timing of initiation of program: inpatient or post hospital discharge.
- Main focus of intervention: parent-infant relationship, infant development, or combined (parent-infant relationship plus infant development).

M E T H O D S

Criteria for considering studies for this review

Types of studies

All trials using random or quasi-random allocation that met the inclusion criteria for types of participant, interventions and outcome were included.

Types of participants

Preterm infants of less than 37 weeks’ gestational age (according to best obstetric estimate at the time of delivery).

Types of interventions

Early developmental intervention programs that aimed to improve cognitive or motor outcome were included. Enrollment in the early intervention programs could occur while the infant was an inpatient during the primary hospitalisation or post-hospital discharge. Intervention had to begin within the first 12 months post-term age and could occur at home, hospital or community centre. Intervention must have been carried out by a health professional, such as a physical therapist, doctor, psychologist or nurse. Types of interventions could include: physical therapy, occupational therapy, psychology, neuro-developmental therapy, parent-infant relationship enhancement, infant stimulation, infant development, developmental care and early intervention (education). These interventions could focus on the parent-infant relationship, infant development, or both.

Types of outcome measures

The following includes some of the possible outcome measures that were used to assess cognitive and motor development.

Cognitive outcome

Continuous


Categorical

Rate of intellectual impairment defined as the number of children scoring more than 2 standard deviations below the mean of the relevant IQ test.

Motor outcome

Continuous

Search methods for identification of studies

The review used the search strategy for the Cochrane Neonatal Review Group. See: Cochrane Neonatal Group, Search strategy for specialised register in The Cochrane Library. A comprehensive search was undertaken by the review authors including Cochrane Central Register of Controlled Trials (CENTRAL, The Cochrane Library, Issue 1, 2006), MEDLINE Advanced (1966 - February 2006), CINAHL (1982 - February 2006), PsychINFO (1966 - February 2006) and EMBASE (1988 - February 2006). The review authors cross referenced relevant literature including identified trials and existing review articles.

The following search strategy was used:
1. infant-premature OR infant-low birth weight
2. AND early intervention (education) OR developmental care OR physical therapy OR occupational therapy OR psychology OR parent-infant relationship OR rehabilitation OR exercise OR neurodevelopmental therapy OR infant stimulation
3. AND child development OR infant development OR cognition OR intellectual disability OR developmental disabilities OR psychomotor performance OR psychomotor disorders OR cerebral palsy OR developmental coordination disorder OR movement disorders OR motor skill disorders
4. NOT drug therapy OR genetics OR chest physiotherapy OR cardiac

Studies that are reported in English or a language for which a translator was available were included.

Data collection and analysis

(i) Inclusion/Exclusion

The standard methods of the Cochrane Neonatal Review Group (CNRG) were used; however, studies where allocation concealment was not used were also included. Eligibility of studies for inclusion were assessed independently by two of the authors who are working in the fields of early intervention and neonatology (AS, JO). The initial search yield was reviewed based upon title and abstract and studies that did not meet the inclusion criteria were excluded. The review authors then evaluated the full text of the remaining articles that appeared to meet the inclusion criteria.

(ii) Methodological quality

Methodological quality of the included trials was evaluated using the CNRG methodological scheme where each article was assessed for selection (blinding of randomisation), performance (blinding of intervention), attrition (completeness of follow up) and detection (blinding of outcome measures). When data were entered into RevMan 4.2 software, allocation concealment was classified as adequate (A), unclear (B), inadequate (C), or was not used (D), as another criterion to assess validity. Additional information was requested from the authors of trials to clarify methodology and obtain missing data (in order to perform analyses on intention-to-treat basis), when necessary. Methodological quality ratings were conducted independently by three review authors (AS, JO, RB). The PEDro (Physiotherapy Evidence Database) Scale adapted from the Delphi Scale was also used to assess quality of the included trials (Verhagen 1998). A point is given for each of the following (maximum score = 11): specification of eligibility criteria, random allocation, allocation concealment, prognostic similarity at baseline, subject blinding, therapist blinding, assessor blinding, greater than 85% follow up of one key outcome, intention to treat analysis, between group statistical comparison of at least one key outcome and reporting of point estimates and measures of variability of at least one key outcome. Sensitivity analysis was conducted using the higher quality studies which had to be randomised trials, and to score at least 7 out of 11 on the PEDro Scale.

(iii) Quantitative analysis

RevMan 4.2 software was used to conduct the data management and analysis. Data were independently entered by two review authors. Standard methods of CNRG were used to synthesise the data. For data analysis “intervention group” refers to infants who were involved in early developmental intervention programs and “follow-up” group refers to infants who had standard medical follow-up. Standard follow-up varied between studies, as different hospitals/ institutions had different standard follow up procedures. For individual trials, where possible, mean values for treatment and control groups (and 95% confidence intervals) were reported for continuous variables. For the meta-analysis of continuous outcomes, standardised mean differences (SMD) were calculated since there were a variety of outcome measures (with different standard deviations) that measure the same outcome. For example, cognitive outcome at infant age can be measured by Bayley MDI or Griffiths GCI. For dichotomous outcomes, the relative risk and risk difference (and 95% confidence intervals) were reported for treatment and follow up groups. Number needed to treat (NNT) was calculated if the risk difference was statistically significant. Cognitive and motor outcome data were pooled into three age groups - infant age (0 - 2 years), preschool age (3 - < 5 years) or school age (5 - 17 years). If studies reported data at more than one time point within an age group, data from the latest assessment was used. For example, if a study reported cognitive outcome at 12 and 24 months, then only the 24 month data were used. Pooled effects for treatment effects were calculated across the trials using a fixed effect model when more than one trial assessed treatment.
effect on the same outcome in similar populations and used similar outcome measures. Heterogeneity was evaluated using the I² statistic. The possible reasons for heterogeneity were explored by scrutinising the studies and, where appropriate, performing subgroup analyses.

RESULTS

Description of studies

See: Characteristics of included studies; Characteristics of excluded studies.

Sixteen randomised or quasi-randomised controlled trials of early developmental interventions post hospital discharge were identified. The search strategy initially retrieved 1,092 references of which 1,035 publications were excluded based upon the title and abstract. The remaining 57 publications required more detailed examination by the two independent review authors. Nineteen publications were excluded from the review as they did not fit all the inclusion criteria (see Table Characteristics of Excluded Studies).

Of the 38 publications that met the inclusion criteria there were only 16 individual trials, since most studies had published several papers related to cognitive and motor outcomes at different ages. The following is a description of each of these 16 studies.

APIP 1998 conducted a multicenter randomised controlled trial comparing two interventions with standard follow-up. All eligible infants (n = 309) born over a two and one-half year period were randomised to one of the three groups at seven to 10 days after birth (Portage = 111, Parent advisor = 99, Follow-up = 99). Consent to participate in the study was obtained post-randomisation to evaluate the acceptability and impact of intervention in population terms. This resulted in the families of 284 infants consenting to participate in the study out of the 309 infants randomly assigned to the 3 groups (Portage = 97, Parent advisor = 90, Standard follow-up = 97). The families of infants who did not consent to the intervention were invited to participate in outcome assessments and outcome data at two years (but not at five years) and results are reported on an intention to treat basis. Both intervention groups were enrolled in a program directed by research nurses at home upon discharge from hospital until two years. Visits were weekly for the first two months, then one to two per month for the next 12 months and then one per month until two years of corrected age. The frequency of visits was tailored to suit the family. The Portage program is a home visiting educational service for children with additional support needs and their families. It takes place in the child’s own home and aims to equip parents with the skills and confidence they will need to help their child. Portage offers practical help and ideas to encourage a child’s interests and make learning fun for the entire family. The primary focus of the Portage group was the developmental progress of the child, although parental support was provided as part of the delivery. A second intervention group was used to control for the parent support given with the Portage group. The parent support group received supportive counseling for parents but no advice on the infant’s development. Details of the care for the standard follow-up group are not given. At two years cognitive development was assessed using the Griffiths GCI, and at five years with the BAS. Motor outcome was assessed at five years with the Movement-ABC. A cut off equivalent to the upper quartile of the term reference group scores was used to defined motor impairment. Rates of cerebral palsy were also reported at five years. All outcomes were measured by a blinded assessor. Data from the two intervention groups were combined and compared with the standard follow-up group for all analyses except for the subgroup analysis of “Focus of Intervention”.

Bao 1999 conducted a multicenter quasi-randomised controlled trial of an intervention package that focused on the infants’ development compared with standard follow-up. Parents of infants in the intervention group (n = 52) were taught to carry out the program, implemented by a doctor, from term equivalent age to two years of age. The program aimed to enhance motor, cognitive and speech development, and to improve social behaviour. The program involved checking the development of the infant and then instructing the parents how to carry out a home program until the next examination. The home program included exercise, suggestion of toys, books and pictorials appropriate to the child’s age. The visits were one per month for the first year and one every two months for the second year. Parent education classes were also reported to occur “sometimes”. Details of the care for the standard follow-up group (n = 51) are not given. Cognitive and motor outcomes were measured at 18 and 24 months using the BSID MDI-II and PDI-II by a blinded assessor.

Barrera 1986 conducted a multicenter randomised controlled trial comparing two types of intervention programs with standard follow-up. Eighty preterm infants were randomly assigned to one of three groups: parent-infant intervention (n = 22), developmental intervention (n = 16) or a standard follow-up (n = 21) group. There were 21 infants who did not complete the study for a variety of reasons (e.g. death of infant, family moved). The number of infants in each group is reported only for the infants who completed the program. The parent-infant intervention aimed to improve the quality of the interaction between the parent and the child by enhancing the parents’ observational skills and teaching them to be mutually responsive to their infant. The developmental program aimed to improve the infants’ cognition, communication, gross and fine motor development, socio-emotional skills and self help skills. Parents worked with therapists to plan and implement developmental activities. Both interventions were implemented by one of four therapists with training in speech pathology, occupational therapy or early childhood education. Sessions were weekly for 3–4 months, bi-weekly for the next six months, and then
conducted a single centre randomised controlled study to assess the effects of early intervention compared with standard follow-up. The intervention group (n = 34) received a physiotherapy program which aimed to improve motor outcome by promoting symmetry, muscle balance and movement using postural support and facilitation techniques. The intervention began while the infant was an inpatient with daily (weekdays) sessions from birth to discharge. It was then provided on a needs-oriented basis post-discharge up to four months. This included advice on play activities to encourage the infant's development based upon the infant's progress. The standard follow-up group (n = 38) received no physiotherapy or placebo interventions. Motor development was assessed at four months using the AIMS, and rates of CP were reported at 18 months by assessors blinded to the child's group allocation.

Cameron 2005 conducted a single centre randomised controlled trial to investigate the effects of a physiotherapy early intervention program compared with standard follow-up. The intervention group (n = 40) received monthly outpatient neurodevelopmental therapy (NDT) at the hospital by a physiotherapist for 12 months. Duration of the treatment was at least 45 minutes, during which time parents were also shown exercises for use at home, where the parents were expected to carry out the program on a daily basis. Infants in both treatment and standard follow-up group (n = 40) were seen at the hospital's follow-up clinic, which was staffed by neonatologists, physiotherapists, speech and hearing therapists, ophthalmologists, public health nurses and social workers, at six weeks, three, six, nine and 12 months' corrected age. In addition to the scheduled visits infants in either group could also attend when clinically indicated. At 12 months and six years of age motor and cognitive development was assessed using the Griffiths GCI and locomotor subscales by a blinded assessor.

The study by I.H.D.P 1990 is the largest multi-centre trial that investigated the effects of early intervention compared with standard follow-up. To minimize the cost of the study, one-third of subjects were randomly assigned to intervention (n = 377) and two-thirds were randomised to standard follow-up (n = 608). The intervention program began post-discharge from the neonatal nursery and continued until 36 months corrected age. The intervention was provided by educational professionals. The intervention group had home visits, attended at a child development centre, and attended parent group meetings. The home visits were weekly for the first year and biweekly for the second and third years. The home visit emphasised cognitive, linguistic and social development via a program of games for the parent to use with the child and aimed to help parents manage self-identified problems. Children in the intervention group attended child development centres 5 days per week, from 12 to 36 months corrected age. Teachers at the centre continued with the above curriculum, taking into account the child's needs and developmental levels. Parent group meetings were held bi-monthly from 12 months, and provided information on child rearing, health and safety and other parental concerns. The standard follow-up group received medical, developmental and social assessments, with referral to other services as indicated. The compliance with the program was variable. The mean number of home visits in the first year = 34.0 (SD 10.2, range 0 - 51); second year = 17.4 (SD 7.2, range 0 - 29) and third year = 15.4 (SD 7.4, range 0 - 26). The mean attendance at child centres for the 2nd year = 132.5 (SD 76.2, range 0-235) and 3rd year = 134.9 (SD 78.5, range 0-241). The mean number of attendees at parent meetings in the 2nd year = 2.1 (SD 1.9, range 0 - 7) and third year...
conducted a randomised controlled trial to evaluate the effect of a physiotherapy motor developmental program in improving motor performance for preterm infants. The 84 infants were classified at risk of developmental delay using the TIMP assessment. The motor developmental program (n = 43) began at 40 weeks postmenstrual age, with a further three visits at one, two and three months corrected age. A physiotherapist instructed the primary care-giver in how to perform three activities with the infant during each session, which were to be carried out at home. Prior to the next visit, the principal researcher evaluated the previous month’s program with the care-giver through an interview and demonstration of the activities by the care-giver. The standard follow up group (n = 41) were assessed (using the TIMP) by a research assistant at one, two, three and four months, and were able to discuss any concerns with the principal researcher. Motor outcome was assessed by a physiotherapist blinded to group allocation at one, two, three and four months’ corrected age using the TIMP.

Melnyk 2001 carried out a quasi-randomised pilot project comparing the “creating opportunities for parent empowerment” (COPE) program with a placebo intervention. The intervention program was carried out in blocks (related to date of admission) so that there was no contamination of the comparison group by staff and parents in the treatment group. The COPE program (n = 26) was a four phase program and consisted of audio-taped, written information and work books on infant behaviour and parental roles. The first three sessions occurred two to four days after admission to hospital and the last session occurred approximately one week after discharge. The comparison program (n = 29) was delivered at the same four time points and involved audio-taped and written information about hospital services, routine discharge information and education about immunizations. Cognitive outcome was measured using the BSID-MDI-II at three and six months by an assessor blinded to infant group allocation.

Nelson 2001 conducted a randomised controlled study to investigate the effects of an infant stimulation program compared with standard follow-up. Infants were randomly assigned to an intervention group (n = 21) or standard follow-up group (n = 16) at 33 weeks of age and were eligible to commence the intervention program after this point. The intervention group received a multisensory stimulation program including auditory, tactile, visual and vestibular stimuli in response to infant behavioural and physiological cues. The intervention was provided by a research assistant in the hospital twice daily, five days per week until discharge. Mothers were taught the intervention, which they continued to administer at home until the infants reached 2 months’ corrected age. The standard follow-up group and the intervention group received a baseline of care in the nursery designed to optimise development, reduce stress, and facilitate both sleep cycles and motor development. All infants also received a home program of physical therapy intervention. Cognitive and motor outcomes were assessed at 12 months using the Bayley MDI-II and PDI-II.

The Mother Infant Transaction Program (MITP), also known as the Vermont Intervention Program by Nurcombe 1984, was a randomised controlled trial comparing the MITP with standard medical follow up. The intervention group (n = 38) received a program designed to enhance mother-infant interaction and infant development by teaching mothers to be more sensitive and responsive to the baby’s physiological, behavioural and social cues. Intervention consisted of a total of 11 sessions delivered by a trained neonatal intensive care nurse. Seven sessions were conducted in hospital prior to discharge and four at home during the first three months following discharge. The initial seven inpatient sessions focused on educating the mother (and father if available) with regard to the infant’s motor system, state regulation, social interaction, daily care and preparing for home. The information given at these sessions was then consolidated in the first session post-discharge. The remaining three sessions at home involved discussion regarding mutual enjoyment through play and understanding of temperamental patterns. Details of the care for the standard follow-up group (n = 40) are not reported. There was a significant difference in the SES between the intervention and standard follow-up groups despite randomisation. The authors reported data that has been adjusted to account for differences in SES. Cognitive and motor outcome was measured at six, 12 and 24 months using the BSID MDI-I and PDI-I. At three and four years cognitive development was assessed using the McCarthy Scale of Children’s Abilities. At seven and nine years cognitive development was assessed using the Kaufman Assessment Battery for Children. All outcome assessors were blinded to the child’s group allocation.

Ohgi 2004 conducted a randomised controlled trial to determine the effect of an early intervention program on preterm infants with a high risk of cerebral palsy compared with standard follow up. The intervention group (n = 12) received a behavioural-based intervention combined with developmental support designed to enhance the infant’s development and parent-infant relationship. The intervention began in the NICU and lasted until six months corrected age. There were two components to the program. The first was designed to facilitate mother-infant interaction and involved three to four, 30 minute sessions, at 36 - 40 weeks’ postmenstrual age, prior to discharge. The second component was focused on advising mothers on how to handle their infant according to the infant’s abilities and developmental needs. The second component was taught to parents during visits at the hospital. After discharge the intervention group had weekly or biweekly outpatient sessions for 40 - 60 minutes. The standard follow-up group (n = 12) had the same care as the treatment group with respect to attendance
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(Review)

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at clinics and referral to developmental services if the infants developed signs of neurological dysfunction or developmental delay. Motor and cognitive outcomes were assessed at six months with the BSID MDI-I and PDI-I by an assessor blind to the infant’s group allocation.

Piper 1986 conducted a randomised controlled trial to assess the effects of early physiotherapy intervention compared with conventional follow up for infants at risk of neurological sequelae. The infants included in the study consisted of two groups - the first were born weighing < 1,500 g and the second were infants with birth asphyxia, seizures or central nervous system (CNS) dysfunction. The preterm intervention group (n = 56) received a 12 month physiotherapy program from 40 weeks postmenstrual age. The outpatient treatment program taught parents specific handling techniques, positioning and stimulation techniques based on neurodevelopmental principles and patterns of movements. All treatment sessions involved individualised treatment, demonstration and parent instruction. For the first three months infants were seen weekly by the same physiotherapist for one hour. For the remaining nine months the infants were seen every two weeks. Individualised written treatment programs were provided to the parent in a notebook and parents were instructed to incorporate handling, positioning and specific exercise routines into activities of daily living. Parents were requested to record in a notebook on a daily basis whether or not they had carried out the activities and any specific problems. The standard follow-up group (n = 59) attended the same neonatal follow-up programs as the intervention group and could be referred to physiotherapy at any time if desired by their paediatrician. Cognitive and motor outcome was measured at 12 months using the Wolanski Gross Motor Evaluation, the Milani-Comparetti Motor Development Screening Test and Griffith Mental Developmental Scales and loco-motor subscale. All outcome assessors were blinded to the child’s group allocation.

Resnick 1988 conducted a quasi-randomised controlled trial designed to evaluate a program of hospital and home-based intervention compared with standard follow-up. Infants in the treatment group (n = 21) had an early childhood development specialist deliver two developmental interventions per day while the infant was in NICU. These interventions involved a stimulation program (auditory, visual, vestibular and tactile) and passive movements. After discharge, a nurse visited the home weekly until term corrected age. From term age until 12 months corrected age an early childhood developmental specialist visited the infant and caregiver twice monthly for one - one and half hour sessions. The post-discharge program focused on language enrichment, social skills, cognitive development, parenting activities and muscular development. The standard follow-up group (n = 20) received a full range of services, including social services, physiotherapy and occupational therapy depending on the baby’s condition. Outcome assessments were made at six and 12 months of age using the BSID MDI-I and PDI-I.

Rice 1979 conducted the first randomised controlled trial of infant stimulation for preterm infants compared with standard follow-up. The intervention group (n = 15) received a tactile-kinesthetic stimulation program administered by their mothers that aimed at enhancing the parent-infant relationship and give infants appropriate levels of stimulation. The program consisted of a stroking treatment for 15 minutes; then the infant was rocked and cuddled for another five minutes. The mother was taught to deliver the intervention by a nurse, four times a day for a period of 30 days beginning the day the infant was discharged from hospital. The standard follow-up group (n = 15) received normal discharge information and was visited regularly (number of visits not reported by authors) by the researcher and by other public health nurses in order to provide social reinforcement for appropriate mothering behaviour. Cognitive and motor development was assessed at four months by an assessor blinded to group allocation using the BSID MDI-I and PDI-I.

Yigit 2002 carried out a randomised controlled trial investigating the effects of early physiotherapy intervention compared with standard follow-up for low-risk preterm infants. The authors do not report how many infants were initially randomised to each group; however, they do report that 39 infants were dropped from the study within the first 12 months due to lack of participation. This resulted in 80 infants in the physiotherapy intervention group and 80 infants in the standard follow-up group at 12 months. The infants were registered for the study prior to hospital discharge; however, it is unclear when the study began. The physiotherapy intervention was based upon the principles of infant stimulation and neurodevelopmental therapy. It is reported that infants attended an early intervention program and were also given a home program; however, no further details of either program are given. It is reported that all study infants were seen by the same physiotherapist once a month for the first nine months, then once every three months until 18 - 24 months old. However, it is unclear whether the physiotherapist provided intervention or assessments at these sessions. No further details of the care for the standard follow up group are reported. Motor outcomes were assessed throughout the intervention based on reflexes and motor milestones and the rates of CP were reported. It is not clear whether assessors were blinded to the infant’s group allocation.

TYPES OF STUDIES

Twelve of the 16 included studies were randomised controlled trials (Rice 1979; Field 1980; Nurcombe 1984; Piper 1986; Barrera 1986; L.H.D.P. 1990; APIP 1998; Lekskulchai 2001; Nelson 2001; Yigit 2002; Ohgi 2004; Cameron 2005), and four were quasi-randomised controlled trials of early developmental programs (Goodman 1985; Resnick 1988; Bao 1999; Melnyk 2001). The randomisation methods for five of the studies was not clear (Rice 1979; Field 1980; Barrera 1986; Nelson 2001; Yigit 2002). For a summary of the included studies see the table ‘Characteristics of Included Studies’.

TYPES OF PARTICIPANTS
All studies included infants who were born preterm. Piper 1986 also included infants who were at high risk of developmental problems due to birth asphyxia. The inclusion criteria for the majority of studies were preterm infants born at < 37 weeks of gestation or born weighing < 2500 g (Rice 1979; Field 1980; Nurcombe 1984; Barrera 1986; I.H.D.P. 1990; Bao 1999; Lekskulchai 2001; Melnyk 2001; Nelson 2001). Four studies included infants born at GA < 34 weeks' or born weighing < 1800 g (Goodman 1985; Resnick 1988; Piper 1986; Yigit 2002) and two studies included infants born at GA < 33 weeks (APIP 1998; Cameron 2005). Two studies included only infants born preterm with cerebral injuries (Nelson 2001; Ohgi 2004).

### TYPES OF INTERVENTION

- **Aim of intervention**

The aim of intervention programs varied between the studies with the majority of programs aiming to improve both cognitive and motor outcomes (Rice 1979; Field 1980; Nurcombe 1984; Piper 1986; Barrera 1986; Resnick 1988; I.H.D.P. 1990; APIP 1998; Bao 1999; Nelson 2001). The main aim of the five studies that involved physical therapy was to improve motor outcomes in the intervention group (Cameron 2005; Goodman 1985; Lekskulchai 2001; Piper 1986; Yigit 2002). Melnyk 2001 aimed to improve only cognitive outcomes in the intervention group.

- **Focus of intervention**

Each study was classified according to the main focus of the intervention program, with possible classifications being “parent-infant relationship”, “infant development” or “infant development and parent-infant relationship”. Enhancing the parent-infant relationship and infant development were the focus of 4 studies (Nurcombe 1984; Resnick 1988; I.H.D.P. 1990; Nelson 2001). Infant development alone was the focus of seven studies (Rice 1979; Goodman 1985; Piper 1986; Bao 1999; Lekskulchai 2001; Yigit 2002; Cameron 2005). One study focused on enhancing the parent-infant relationship alone (Melnyk 2001). Two studies had two intervention groups and a control group. Barrera 1986 had one group that received a parent-infant focused intervention and the other received an infant development focused intervention, while APIP 1998 had one group that received an infant development intervention and one group that received “parent support”. An additional classification of “parent support” was added in for this study.

- **Types of intervention**

Although the focus of the intervention programs was to improve cognitive and/or motor outcomes, the theoretical constructs and components of the intervention programs varied greatly. The programs were implemented by doctors (Bao 1999), physiotherapists (Piper 1986; Goodman 1985; Lekskulchai 2001; Yigit 2002; Cameron 2005), nurses (Rice 1979; Nurcombe 1984; Resnick 1988; APIP 1998), intervention therapists (Nurcombe 1984), education professionals (I.H.D.P. 1990; Resnick 1988) or occupational therapists and speech pathologists (Barrera 1986). The theoretical constructs of intervention programs included teaching parents about infant development and milestones (Barrera 1986; Resnick 1988; I.H.D.P. 1990; Bao 1999; Ohgi 2004; Cameron 2005), understanding behavioural cues (Nurcombe 1984; Barrera 1986; Bao 1999; Melnyk 2001; Ohgi 2004; Cameron 2005), infant stimulation (Rice 1979; Field 1980; Nurcombe 1984; Nelson 2001), physical therapy (Goodman 1985; Piper 1986; Lekskulchai 2001; Nelson 2001; Yigit 2002; Cameron 2005), early educational intervention (I.H.D.P. 1990; Bao 1999), and the enhancement of the parent-infant relationship (Field 1980; Nurcombe 1984; Resnick 1988; I.H.D.P. 1990; Melnyk 2001; Ohgi 2004).

- **Frequency of intervention**

The frequency and duration of the intervention programs ranged from four sessions over approximately one month (Melnyk 2001), to weekly sessions for 12 months, followed by bi-weekly sessions for a further two years (IHDP 1990). The majority of the interventions began post-discharge from hospital (Rice 1979; Field 1980; Goodman 1985; Barrera 1986; Piper 1986; I.H.D.P. 1990; APIP 1998; Bao 1999; Lekskulchai 2001; Yigit 2002), while four studies began when the infant was still an inpatient (Nurcombe 1984; Resnick 1988; Ohgi 2004, Cameron 2005).

### TYPES OF OUTCOME MEASURES

- **Cognitive outcome**

Thirteen studies reported on cognitive outcome.
- At infant age (0 - 2 years) seven studies reported cognitive outcome using the BSID-MDI I (Rice 1979; Field 1980; Nurcombe 1984; Barrera 1986; Resnick 1988; I.H.D.P. 1990; Bao 1999), three with the BSID-MDI II (Melnyk 2001; Nelson 2001; Ohgi 2004) and three with Griffiths Development Mental Development Scale (Goodman 1985; Piper 1986; APIP 1998).
- At preschool age (3 - <5 years) three studies reported cognitive outcome using either the Stanford-Binet Intelligence Scale (IHDP 1990) or McCarthy Scales of Children’s Abilities (Barrera 1986; Nurcombe 1984).
- At school age (5 - 17 years) four studies reported cognitive outcome using either the WPPSI and WISC-III (IHDP 1990), Kaufman Assessment Battery for Children - Mental Processing Composite (Nurcombe 1984), Griffiths Mental Development Scale (Goodman 1985), and the British Ability Scale (APIP 1998).
- No studies reported the incidence of intellectual impairment.

- **Motor outcome**

Fifteen studies reported on motor outcomes using a wide variety of outcome measures at different ages.
- At infant age 13 studies reported motor outcomes using standardised measurement tools including the BSID-PDI-I (Rice 1979; Field 1980; Nurcombe 1984; Barrera 1986; Resnick 1988; I.H.D.P. 1990; Bao 1999), BSID-PDI-II (Nelson 2001; Ohgi 2004), Griffiths Locomotor Subscale (Goodman 1985; Piper 1986), Test of Infant Motor Performance (Lekskulchai 2001) and Alberta Infant Motor Scale (Cameron 2005). An additional study
(Yigit 2002) reported on the age of acquisition of motor skills such as sitting and crawling.
- No studies reported on motor outcomes at preschool age.
- At school age two studies reported motor outcome using either the Movement ABC (APIP 1998) or the Griffiths Locomotor subscale (Goodman 1985).
- The rate of cerebral palsy was reported by four studies (Goodman 1985; APIP 1998; Yigit 2002; Cameron 2005).
- No studies reported on the rate of developmental co-ordination disorder, however, one study did report on the number of children classified as having a motor impairment (APIP 1998).

Risk of bias in included studies

CONCEALMENT OF ALLOCATION
Of the 16 studies, seven had adequate concealment of allocation (I.H.D.P. 1990; APIP 1998; Lekskulchai 2001; Nurcombe 1984; Ohgi 2004; Piper 1986; Cameron 2005), five studies did not clearly state randomisation methods (Rice 1979; Field 1980; Barrera 1986; Nelson 2001; Yigit 2002) and the remaining studies did not use adequate methods of allocation concealment (Goodman 1985; Resnick 1988; Bao 1999; Melnyk 2001).

BLINDING OF INTERVENTION
Melnyk 2001 was the only study that had a comparison treatment group and, therefore, the only study that may have blinded the participants to the intervention. APIP 1998 had two intervention groups, one that received a developmental intervention and one that received parent support only, to control for the parent support component of an intervention that occurs with any family contact. Barrera 1986 also had two intervention groups; however, this was a comparison of two types of intervention. All other studies involved comparison of the intervention program with standard follow up and, therefore, families were not blinded to the intervention. No studies report masking of the therapists delivering the interventions. Masking of the therapists delivering the interventions is often not feasible unless there is a program similar to the one in the study by Melnyk 2001, where the content of the intervention is delivered through audio-tape and written material.

COMPLETENESS OF FOLLOW UP
The completeness of follow up varied greatly both within and between studies. Eight studies had greater than 85% follow up at one time point (Field 1980; Nurcombe 1984; Piper 1986; I.H.D.P. 1990; APIP 1998; Bao 1999; Lekskulchai 2001; Ohgi 2004). It was difficult to assess the completeness of follow up of some studies since the initial number of subjects participating in the trials was not clearly stated (Rice 1979; Piper 1986; Barrera 1986; Resnick 1988). Studies that began in the NICU had a greater potential for lower follow up rates, since the survival of infants was not always as apparent as when infants were recruited post-hospital discharge. For example, Cameron 2005 began the intervention program in hospital and had only 83% follow up at four months of age, as 7% (five infants) of infants in the study died prior to the first outcome assessment at four months. Goodman 1985 stopped their study after there were 20 infants in four subgroups who had completed the study, despite enrolling 107 infants.

BLINDING OF OUTCOME MEASURES
All studies had at least one blinded outcome measure except for Yigit 2002, where it is unclear whether the assessors were blinded to the subjects’ intervention status.

FURTHER QUALITY ASSESSMENT
Seven studies were considered to be of higher quality, scoring at least seven out of 11 using the PEDro scale of methodological quality (Nurcombe 1984; I.H.D.P. 1990; APIP 1998; Lekskulchai 2001; Melnyk 2001; Ohgi 2004; Cameron 2005). All of these studies, except for the study by Melnyk 2001, were randomised trials and, therefore, considered as the higher quality studies in the sensitivity analysis. The highest quality studies were the trials by IHD 1990 and APIP 1998, which scored 9/11 on the PEDro scale, followed by Lekskulchai 2001; Nurcombe 1984 and Ohgi 2004 which scored 8/11, followed by Melnyk 2001 and Cameron 2005 which scored 7/11. All studies specified their inclusion criteria except for Bao 1999 who only indicated that infants were born at less than 37 weeks GA. All studies had similar prognostic characteristics of intervention and controls at baseline related to perinatal factors such as gestational age; however, some studies reported differences in socio-demographic variables (Nurcombe 1984; APIP 1998). Intention to treat analysis was only specified in the studies by IHDP 1990; APIP 1998 and Melnyk 2001. Piper 1986 and Barrera 1986 did not report point estimates and measures of variability for the preterm infants in their respective studies for cognitive or motor outcomes and, therefore, these studies could not be included in the meta-analysis.

Effects of interventions

This review found 16 quasi-randomised or randomised controlled trials involving 2408 infants. The primary objective was to determine the effect of early developmental intervention programs post hospital discharge for preterm infants on cognitive and motor development compared with standard medical follow-up at infant (0 - 2 years), preschool (3 - <5 years) and school ages (5 - 17 years).

EARLY DEVELOPMENTAL INTERVENTION VS. STANDARD FOLLOW UP (All studies) (COMPARISON 01) Cognitive outcome at infant age (Outcome 01.01):
Eight studies reported sufficient data on cognitive outcome to be pooled for meta-analysis. Infants who received early developmental intervention (n = 670) scored a standardized mean DQ of 0.46 SD (95% CI 0.36; 0.57; P < 0.001) higher than infants who received standard follow up (n = 774). Of the 8 studies, only three studies (I.H.D.P. 1990; Bao 1999; Melnyk 2001) showed a statistical significance in favour of the treatment group, while the other studies showed a non-statistical difference in favour of the intervention group (Nurcombe 1984; Goodman 1985; APIP
There was significant heterogeneity between the studies ($I^2 = 63.4\%$) that reflects the diversity in the early intervention programs but limits the conclusions of these results. An additional four studies did not provide adequate data for meta-analysis. Two of these studies reported a significant difference in favour of the intervention group (Rice 1979; Field 1980) and two found no difference (Barrera 1986; Piper 1986). Rice 1979 reported a significant difference ($P < 0.05$) in favour of the intervention group ($n = 15$) at four months of age compared with the control group ($N = 15$) on the BSID-I; however, means and standard deviations were not reported. Field 1980 reported the intervention group ($n = 27$) scored a mean of nine DQ points higher than the control group ($n = 25$) on the BSID-I at eight months; however, standard deviations were not reported ($P < 0.001$).

Cognitive outcome at preschool age (Outcome 01.02): Three studies reported cognitive outcome and these data were pooled for meta-analysis. At preschool age, children who received early developmental intervention as infants ($n = 403$) had a standardized mean IQ of 0.46 SD (95% CI 0.33, 0.59; $P < 0.001$) higher than children who received standard follow up ($n = 603$). Two studies reported a significant difference favouring the intervention group (Nurcombe 1984; I.H.D.P. 1990) and the other study found no difference between groups (Barrera 1986).

Cognitive outcome at school age (Outcome 01.03): Three studies reported sufficient data for meta analysis (Nurcombe 1984; I.H.D.P. 1990; APIP 1998). At school age, children who received early developmental intervention ($n = 484$) did not score significantly higher than the children who received standard follow up ($n = 627$) on IQ measures (IQ; SMD 0.02 SD; 95% CI -0.10, 0.14; $P = 0.71$). Of the three studies, only Nurcombe 1984 reported a significant difference in favour of the intervention group, however, this study had a small sample size ($n = 55$). There was significant heterogeneity ($I^2 = 84.1\%$) between the studies that limits the conclusions that can be made from these results. Goodman 1985 also reported that there was no difference between intervention and standard follow-up groups when cognitive outcome was measured on the Griffiths GCI.

Motor outcome at infant age (Outcome 01.04): Six studies provided sufficient data for meta analysis with the Bayley PDI and one with the Griffiths Locomotor Subscale. There was no difference in motor outcome for infants who received early developmental intervention ($n = 477$) compared with infants who received standard follow up ($n = 672$), (DQ: SMD 0.05 SD; CI 95% -0.06, 0.17; $P = 0.37$). None of the six studies found a significant difference between intervention and standard follow-up (Nurcombe 1984; Goodman 1985; I.H.D.P. 1990; Bao 1999; Nelson 2001; Ohgi 2004). An additional seven studies reported motor outcomes; however, these studies were not appropriate for use in meta-analysis (due to type of assessment tool or missing data). Of these studies, Lekskulchai 2001 was the only study that reported a significant difference in favour the intervention group ($P < 0.001$) using the Test of Infant Motor Performance at four months of age. The remaining six studies found no difference at infant age.

Motor outcome at school age (Outcome 01.05): No studies reported motor outcomes at preschool age.

Motor outcome at school age (continuous variables) (Outcome 01.06): Goodman 1985 was the only study to report motor outcomes using the Griffith locomotor scale at six years of age and there was no difference in motor outcomes for children who received early intervention (SMD: -0.34; 95%CI -0.91,0.23; $P = 0.25$).

Motor outcome at school age (dichotomous variables) (Outcome 01.07): APIP 1998 reported the number of children with motor impairments at five years using the Movement ABC. A cut off equivalent to the upper quartile of the term reference group scores was used to define motor impairment. There was no difference in motor outcome for children who received early intervention (typical RR 1.04; 95%CI 0.78, 1.38; $P=0.79$).

Rate of cerebral palsy (Outcome 01.08): Four studies reported rates of cerebral palsy (Goodman 1985; APIP 1998; Yigir 2002; Cameron 2005). There was no difference in the relative risk of cerebral palsy between intervention and standard follow-up (typical RR 0.95; 95% CI 0.57, 1.58; $P = 0.84$).

SUBGROUP ANALYSIS: GESTATIONAL AGE (COMPARISON 02)

Cognitive outcome at infant age (Outcome 02.01): The majority of studies used infants born at a wide range of gestational ages and did not report outcomes related to subgroups of gestational age. The only study that investigated the impact of GA on the effect of early developmental intervention was the study by APIP 1998. They reported that infants born at GA<28 (DQ: SMD 0.39; 95%CI -0.06, 0.84; $P = 0.09$) benefited more from the intervention program than infants born at GA > 28 weeks at infant age (DQ: SMD 0.09; 95%CI -0.25, 0.43; $P = 0.60$); however, the effect for both subgroups was not statistically significant.

Cognitive outcome at preschool age: No studies reported outcomes in relation to gestational age.

Cognitive outcome at school age: No studies reported outcomes in relation to gestational age.

Motor outcome at infant age: No studies reported outcomes in relation to gestational age.

Motor outcome at preschool age: No studies reported outcomes in relation to gestational age.

Motor outcome at school age (continuous variables): No studies reported outcomes in relation to gestational age.

Motor outcome at school age (dichotomous variables): No studies reported outcomes in relation to gestational age.
Rate of cerebral palsy:
No studies reported outcomes in relation to gestational age.

**SUBGROUP ANALYSIS: BIRTHWEIGHT (COMPARISON 03)**

**Cognitive outcome at infant age (Outcome 03.01):**

Three studies investigated the impact of birthweight on the effect of early developmental interventions. However, only one of these studies (Barrera 1986) used the birthweight subgroups of LBW (1500 - 2499 g), VLBW (1000 - 1499 g) and ELBW (< 1000 g). Barrera 1986 carried out subgroup analysis of heavier infants (1500 - 1999 g) and lighter infants (< 1500 g) and reported that infants born at LBW in both intervention groups had significant therapeutic gains compared with the higher birth weight infants at infant age. However, they did not report means and standard deviations. I.H.D.P. 1990 analysed the results of a higher weight subgroup (BW > 2000 g) and a lower weight subgroup (BW < 2000 g) and reported that infants born at higher birth weights benefited more from the intervention program. The heavier infants who received intervention (n = 125) scored 0.75 of a SD (95% CI 0.52, 0.98; P < 0.001) higher than heavier infants who had standard follow up (n = 197), whereas there was no difference in outcome between infants born at lighter birthweights (n = 218) who received intervention or standard follow up (n = 355). This data could not be added to the meta-analysis because the weight categories were different. APiP 1998 reported data for infants born at higher birth weights (> 1250 g) and lighter birthweights (< 1250 g). They found that the lighter birthweight infants who were in the “portage group” (n = 22) scored 5.3 DQ points (95% CI 0.2, 10.2; P < 0.05) higher than infants in the control group (n = 29), whereas there was no difference between infants in the heavier subgroup who had intervention or standard follow up at 12 months. There is conflicting evidence about benefits of early developmental interventions according to birthweight.

**Cognitive outcome at preschool age (Outcome 03.02):**

The study by I.H.D.P. 1990 was the only study to report outcomes according to birthweight at preschool age. At preschool age the higher birth weight infants who received intervention scored 0.70 of a SD (95% CI 0.47, 0.93; p < 0.001) higher than infants who had standard follow up. Lighter weight infants who received intervention scored 0.33 of a SD (95% CI 0.16, 0.50; P < 0.001) higher than infants who received standard follow-up.

**Motor outcome at school age:**

I.H.D.P. 1990 reported no difference in motor outcome between intervention and control groups who were born at heavier (> 2000 g) or lighter (< 2000 g) weights at infant age. Barrera 1986 also reported no difference in motor outcome between intervention and control groups born at heavier (1500 - 1999 g) or lighter (< 1500 g) weights at infant age.

**Motor outcome at preschool age:**

No studies reported motor outcomes in relation to birthweight.

**Motor outcome at school age (continuous variables):**

No studies reported motor outcomes in relation to birthweight.

**Motor outcome at school age (dichotomous variables):**

No studies reported outcomes in relation to birth weight.

**Rate of cerebral palsy:**

No studies reported outcomes in relation to birth weight.

**SUBGROUP ANALYSIS: BRAIN INJURY (COMPARISON 04)**

**Cognitive outcome at infant age (Outcome 04.01):**

Most of the included studies did not report separate results for infants who had PVL or IVH. Two studies only included infants who were at risk of adverse neurological outcomes due to periventricular leukomalacia and/ or intraventricular haemorrhage (Nelson 2001; Ohgi 2004). These two studies did not demonstrate a significant difference in cognitive outcome of the intervention and control groups born at infant age (DQ; SMD 0.5; 95%CI -0.12, 1.13; P = 0.11). The only study that reported the cognitive outcome for infants in the intervention and control groups who had abnormal ultrasound results compared with those with normal ultrasound results was the study by APiP 1998. They reported that infants who were at risk of adverse neurological outcome had a significant benefit from early developmental intervention, whereas those infants who were not at-risk did not show any cognitive benefits from the intervention program.

**Cognitive outcome at preschool age:**

No studies reported cognitive outcome in relation to brain injury.

**Cognitive outcome at school age:**

APiP 1998 was the only study that reported outcomes in relation to normal and abnormal ultrasound findings and reported that there was no difference between groups at school age.

**Motor outcome at infant age (Outcome 04.02):**

The studies by Ohgi 2004 and Nelson 2001 included infants who were at risk of adverse neurological outcomes due to PVL and/ or IVH and did not demonstrate a significant difference between intervention and follow-up groups (DQ; SMD 0.47; 95% CI -0.15, 1.10; P = 0.14). The standard follow-up groups in both of these studies had access to physiotherapy services as required.

**Motor outcome at preschool age:**

No studies reported motor outcome in relation to brain injury.
Motor outcome at school age (continuous variables): No studies reported motor outcome in relation to brain injury.

Motor outcome at school age (dichotomous variables): No studies reported outcomes in relation to brain injury.

Rate of cerebral palsy: No studies reported outcomes in relation to brain injury.

**SUBGROUP ANALYSIS: COMMENCEMENT OF INTERVENTION PROGRAM (INPATIENT VS. POST HOSPITAL DISCHARGE) (Comparison 05)**

Cognitive outcome at infant age (Outcome 05.01): Of the eight studies that reported sufficient data for meta-analysis, four began when the infants were in the NICU (Nurcombe 1984; Melnyk 2001; Nelson 2001; Ohgi 2004) and four began post-hospital discharge (Goodman 1985; I.H.D.P. 1990; APIP 1998; Bao 1999). The programs that began while the infants were inpatient had a significant impact on cognitive outcome at infant age (DQ; SMD 0.55; 95%CI 0.22, 0.89; P = 0.001), as did the programs that commenced post hospital discharge (DQ; SMD 0.45; 95%CI 0.34, 0.57; P < 0.001) compared with standard follow-up. Interventions that commenced in the NICU were statistically homogeneous (I² = 0%), whereas there was significant heterogeneity between the interventions that commenced post hospital discharge (I² = 83.6%). Interventions that commenced while the infant was in-hospital were more similar in focus of and intensity of intervention, whereas the only interventions to have a significant effect post discharge were the studies by I.H.D.P. 1990 and Bao 1999. The IHDP study had much larger subject numbers and was greater in intensity than any other program.

Cognitive outcome at preschool age (Comparison 05.02): There was only one study that began in the NICU (Nurcombe 1984) and it reported a significant effect in favour of the intervention group (IQ; SMD 0.79; 95%CI 0.23, 1.35; p = 0.006). Of the two studies that began post-discharge, Barrera 1986 reported no difference between groups, whereas I.H.D.P. 1990 reported a significant difference in favour of the intervention group (IQ; SMD 0.44; 95%CI 0.31, 0.57; p < 0.0001). Due to the much larger sample size of the study by I.H.D.P. 1990 (n = 908) compared to the study by Barrera 1986 (n = 45) there was an overall effect in favour of the intervention group; however, there is significant heterogeneity (I² = 58%) that limits the conclusions of these results.

Cognitive outcome at school age (Outcome 05.03): The study by Nurcombe 1984 is the only study that began in the NICU and reported school age outcomes. This study reported that school age children who had intervention that began as inpatient had a significantly higher IQ scores than those infants who received standard follow up (IQ; SMD 1.02; 95% CI 0.45, 1.59, P < 0.001). The two studies that began post-hospital discharge did not demonstrate a difference between outcomes. The sample size of the study in which interventions began in the NICU (n = 55) is much smaller than the sample size of the studies where interventions that began post-hospital discharge (n = 1056).

Motor outcome at infant age (Outcome 05.04): Of the studies that provided sufficient data for meta-analysis, three began when the infants were in the NICU (Nurcombe 1984; Nelson 2001; Ohgi 2004) and three began post-hospital discharge (Goodman 1985; I.H.D.P. 1990; Bao 1999). The programs that began post-hospital discharge had a slightly greater impact on motor outcome at infant age (DQ; SMD 0.06; -0.06, 0.19; P = 0.32) than the programs that began while the infants were in the NICU (DQ; SMD -0.03; 95%CI -0.39, 0.33, P = 0.88); however, neither group showed a significant effect.

Motor outcome at preschool age (outcome 05.05): The study by Goodman 1985 began post-hospital discharge and did not show any difference between groups.

Motor outcome at school age (continuous variables) (Outcome 05.06): The study by APIP 1998 was the only study to report rates of motor impairment and there was no difference between groups.

Rate of cerebral palsy (Outcome 05.08): The study by Cameron 2005 was the only study to begin in the NICU and report rates of CP and there was no difference between groups. The three studies by Goodman 1985; APIP 1998 and Yigit 2002 began post-hospital discharge and also found no difference in rates of CP between groups.

**SUBGROUP ANALYSIS: FOCUS OF INTERVENTION (PARENT-INFANT RELATIONSHIP VS. INFANT DEVELOPMENT VS. COMBINATION) (COMPARISON 06)**

Cognitive outcome at infant age (Outcome 06.01): The primary focus of one study was on the parent-infant relationship (Melnyk 2001). Infants who received early intervention that focused on the parent-infant relationship alone scored a standardised mean DQ of 0.73 SD (95%CI 0.11, 1.36, P = 0.02) higher than infants who received standard follow up. Three studies primarily focused on the infants development (Goodman 1985; APIP 1998; Bao 1999). Of these three studies, only one study reported a significant difference in favour of the intervention group (Bao 1999), while the other two studies reported a trend in favour of the treatment group. Overall, infants who received intervention that focused on infant development scored a standardised mean DQ of 0.39 SD (95%CI 0.17, 0.61; P < 0.001) higher than infants who received standard follow up. However, there was significant heterogeneity (I² = 87.2%) between these studies that reflects the diversity in early intervention programs that focus on the infants development. There were four studies that focused on both the parent-infant relationship and infant development (Nurcombe 1984; I.H.D.P. 1990; Nelson 2001; Ohgi 2004). The I.H.D.P. 1990...
was the only study to report a significant difference in favour of the intervention group, whereas the other studies reported a trend in favour of the treatment group. Overall, infants who received intervention that focused on both parent-infant relationship and infant development scored a standardized mean DQ of 0.51 SD (95% CI 0.38, 0.64; P < 0.001) higher than infants who received standard follow up at infant age. The study by APIP 1998 investigated the effect of parent support or infant development (with parent support) compared to standard follow-up and reported no difference between groups.  

**Cognitive outcome at preschool age (Outcome 06.02):**  
At preschool age there were two studies (Nurcombe 1984; I.H.D.P. 1990) that focused on both the parent-infant relationship and infant development together and one study (Barrera 1986) that had two intervention groups. In the study by Barrera 1986, one treatment group focused on infant development and the other intervention group focused on parent-infant relationship. Only the pooled results of the two different intervention groups were reported by Barrera 1986 and, therefore, were not included. Infants who received intervention that focused on both parent-infant relationship and infant development scored a standardized mean IQ of 0.48 SD (95% CI 0.35, 0.61; P < 0.001) higher than infants who received standard follow up at preschool age.  

**Cognitive outcome at school age (Outcome 06.03):**  
At school age there were two studies that had focused on parent-infant relationship and infant development (Nurcombe 1984; I.H.D.P. 1990) and one study that had two intervention groups (APIP 1998). The two studies that focused on both the parent-infant relationship and infant development had different results, with the study by I.H.D.P. 1990 showing no effect and the study by Nurcombe 1984 showing a significant different in favour of the intervention group. There is significant heterogeneity (I² = 96%) due to the difference in sample size and outcomes of these studies. Overall there was no significant difference at school age in the cognitive development of children who received any of the four types of early intervention programs compared with children who received standard follow up as infants.

**Motor outcome at infant age (Outcome 06.04):**  
Studies that reported on motor outcome at infant age either focused on both parent-infant relationship and infant development (Nurcombe 1984; I.H.D.P. 1990; Nelson 2001; Ohgi 2004) or on the infants’ development alone (Goodman 1985; Bao 1999). Programs that focused on infant development had a slightly greater impact on motor outcome at infant age (DQ: SMD 0.26 SD; 95% CI -0.05, 0.58; P = 0.1) than those that focused on the parent-infant relationship and infant development together (DQ: SMD 0.02 SD; 95% CI -0.11, 0.15, P = 0.76); however, the effect of both groups was not significant.  

**Motor outcome at preschool age:**  
No studies reported on motor outcome at preschool age.

**Motor outcome at school age (continuous variables) (Outcome 06.05):**  
The study by Goodman 1985 focused on infant development and there was no significant difference between groups.

**Motor outcome at school age (dichotomous variables):**  
The study by APIP 1998 focused on infant development and reported no difference between groups.

**Rate of cerebral palsy (Outcome 06.06):**  
The four studies that reported rates of CP focused on infant development and reported no difference between groups (Goodman 1985; APIP 1998; Yigit 2002; Cameron 2005).

**SUBGROUP ANALYSIS: QUALITY OF STUDIES (HIGHER vs LOWER) (COMPARISON 07)**

**Cognitive outcome at infant age (Outcome 07.01):**  
Four of the studies included in meta-analysis were of high quality (Nurcombe 1984; I.H.D.P. 1990; APIP 1998; Ohgi 2004) and reported a significant treatment effect supporting the intervention group (IQ: SMD 0.44 SD; 95% CI 0.32, 0.56; P < 0.001). There was less heterogeneity between the higher quality studies, than when all studies were included in the meta-analysis.

**Cognitive outcome at preschool age (Outcome 07.02):**  
At preschool age two (Nurcombe 1984; I.H.D.P. 1990) of the three studies were high quality; again, a significant treatment effect supporting the intervention group was demonstrated (IQ: SMD 0.48 SD; 95% CI 0.35, 0.61; P < 0.001).

**Cognitive outcome at school age (Outcome 07.03):**  
At school age the studies were all of high quality and, therefore, no subgroup analysis was necessary.

**Motor outcome at infant age (Outcome 07.04):**  
Three studies were of high quality (Nurcombe 1984; I.H.D.P. 1990; Ohgi 2004) and reported no significant difference between groups (SMD 0.01 SD: -0.12, 0.14, p = 0.87).

**Motor outcome at preschool age:**  
No studies reported motor outcomes.

**Motor outcome at school age (continuous) (Outcome 07.05):**  
There were no high quality studies that reported motor outcomes.

**Motor outcome at school age (dichotomous) (Outcome 07.06):**  
APIP 1998 was the only high quality study to report rates of motor impairment and there was no difference between groups.

**Rate of cerebral palsy (Outcome 07.07):**  
APIP 1998 and Cameron 2005 were the only two high quality studies to report rates of cerebral palsy and found no difference between groups.

**DISCUSSION**

The primary goal of this current review was to determine the effect of early developmental intervention programs post-discharge
Early developmental intervention programs post hospital discharge to prevent motor and cognitive impairments in preterm infants (Review)

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from hospital for preterm infants on cognitive and motor development compared with standard medical follow-up at infant (0 - 2 years), preschool (3 - < 5 years) and school age (5 - 17 years). There were 16 randomised or quasi randomised controlled trials of early developmental interventions for preterm infants included in the review; however, not all studies provided sufficient data to be included in the meta-analysis. Meta-analysis demonstrated a treatment effect for early intervention on cognitive outcomes at infant and preschool age of approximately half a standard deviation on standardised cognitive tests. The size of the effect is considered to be of clinical significance. Meta analysis indicates that intervention did not have a significant effect on motor outcome up to two years of age, or in the two studies that reported on long-term motor outcomes.

There has been considerable debate as to how best to reduce or prevent long term impairments and improve the cognitive and motor outcomes for children born preterm. To our knowledge, this is the first reported meta-analysis of early developmental interventions post-discharge from hospital for preterm infants. Blauw-Hospers 2005 recently published a systematic review investigating the effects of early intervention on motor outcomes for all infants at risk, or with developmental motor disorders. They defined early intervention as “multidisciplinary services provided to children from birth to five years of age to promote child health and well-being, enhance emerging competencies, minimize developmental delays, existing or emerging disabilities, prevent functional deterioration, and promote adaptive parenting and overall family functioning”. They reported that NIDCAP, an inpatient program using interventions that focus on specific motor training such as treadmill training or general development programs that aim to increase the child’s exploration, have a positive effect on motor outcomes for high risk infants. Blauw-Hospers 2005 systematic review was broader than this review since it included all early intervention programs that began from birth to 18 months for all infants at risk for, or with developmental motor disorders and, therefore, it was not appropriate for meta-analysis to be performed. They did not include preterm infants at “low risk” of developmental motor disorders and, therefore, many of the studies included in this review are not included by Blauw-Hospers 2005. The inclusion criteria for early developmental interventions programs in this review was very specific in an attempt to limit the variability in intervention programs. As Blauw-Hospers 2005 reported in their systematic review, the term “early intervention” can be understood in two-ways, intervention that occurs early in life, or intervention that occurs early in the expression of the condition. We have only included intervention programs that began early in life, within the first 12 months when the brain is highly plastic (Hadders-Algra 2001). These intervention programs are more likely to be prevention programs since specific problems that require “treatment” are less likely to be apparent.

There are a number of limitations of this review and in the performance of meta-analysis with studies on early developmental intervention. The programs of early developmental intervention that the “treatment groups” received in this review varied in theoretical content, environmental context, intensity and duration of follow up. This resulted in significant levels of heterogeneity when pooling cognitive outcomes and, therefore, limits the conclusions that can be drawn from these results. Subgroup analysis was useful to investigate areas of variation between the trials. The majority of included studies recruited infants in the 1980s when the mean gestational age at entry was older than studies conducted in the 1990s. Advances in perinatal care mean that medical interventions received by infants may not be the same across studies, and pooling results across eras may result in comparing different groups of infants with respect to outcomes. However, rates of neurosensory morbidity have remained relatively constant over the past two decades, compared with rates of mortality that have decreased (Doyle 2004). To account for the difference in gestational age and birthweights of infants across studies, subgroup analysis was planned for both of these factors. The majority of studies did not report the outcomes according to gestational age or birthweight and, therefore, subgroup analysis was limited. I.H.D.P. 1990 reported that infants who were born between 2000 - 2500 g had a greater response to intervention. The studies by Barrera 1986 and APIP 1998 found the opposite response, with infants born at very low birth weights having a greater cognitive response at infant age. No studies reported a difference in motor outcome between intervention and control groups related to gestational age or birthweight. The presence of brain injury is also important to consider when assessing the effect of intervention for preterm infants. Only two studies included infants with periventricular leukomalacia or intraventricular haemorrhage and these studies reported no difference in cognitive and motor outcome between intervention and control groups (Nelson 2001; Ohgi 2004). The standard follow-up group in both of these studies received physiotherapy as required, which may have affected the motor outcomes of these infants. The study by APIP 1998 reported that infants with abnormal cranial ultrasound findings had a positive cognitive response to intervention, whereas there was no difference in outcome between the infants who had intervention or standard follow up with normal cranial ultrasound. The other studies did not report whether they excluded infants with abnormal imaging, PVL or IVH and, therefore, could not be included in the subgroup analysis.

Other perinatal variables such as socio-economic status (SES) are also important to consider when comparing different studies. The studies by Rice 1979 and Field 1980 only included infants who were born to mothers of low SES. Both of the studies by APIP 1998 and Nurcombe 1984 had significant differences in SES between groups despite randomisation. The control group in the study by APIP 1998 had a higher percentage of mothers who were educated beyond 16 years of age, were in non-manual occupations and had use of a car compared with the intervention groups. All
three of these variables were independently associated with Griffiths quotients and may explain part of the variance in outcome. Using a regression model to account for the SES differences between groups, the authors report an improvement in IQ scores of both the portage and parent advisor groups compared with the standard follow-up group. The study by Nurcombe 1984 reported that results were adjusted to account for the difference in SES between groups. The studies by Field 1980 and Rice 1979 included only families of low SES, which limits the generalisability of the results to the general population.

Two types of subgroup analyses were performed in relation to the types of intervention programs. The first subgroup analysis compared interventions that were begun while the infant was still in hospital with those that were begun post-hospital discharge. Both types of programs had a significant effect on cognitive outcome at infant and preschool age. At school age, the only study to demonstrate a difference in favour of the intervention group began as an inpatient; however, this study (Nurcombe 1984) had small subject numbers and low follow-up rates. The interventions that began when the infants were inpatients were homogeneous, since they all focused on the parent-infant relationship and enhancing the parents’ abilities to read and respond appropriately to their infants’ behavioural cues. There was significant heterogeneity between the interventions that occurred post-hospital discharge, which can be explained by the variety of intervention programs. Interventions that began post-hospital discharge had a greater impact on motor outcome in infants; however, the effect was not significant. The second subgroup analysis related to the focus of the intervention program being the parent-infant relationship, infant development or both. Interventions that had a component that focused on the parent-infant relationship had a greater impact on cognitive outcome at infant and preschool ages than interventions that focused on infant development or parent support alone. Although interventions that focused on infant development alone had a greater impact on motor development, the effect was not significant and the studies were of lower quality.

This review has compared early developmental interventions with standard follow-up; however, details of standard follow-up were not always reported. Many of the studies that reported details of follow-up reported that infants and families still had access to developmental services such as physiotherapy and social services. Although there is limited evidence for some of these services (Wang 2006), it may be unethical to prevent access to them. The services received by the standard follow-up group may improve their outcomes and, therefore, a treatment effect may be more difficult to detect. For example, the standard follow-up group in five studies (Goodman 1985; Piper 1986; Resnick 1988; Nelson 2001; Ohgi 2004) received physiotherapy in accordance with the institutions’ policies, which may have influenced the motor outcomes of the standard follow-up group. Contamination of the control and intervention groups with additional treatments or other therapies is also problematic, as families of preterm infants may seek additional treatments for their child who is perceived to be “at risk” of developmental difficulties. None of the studies reported the “dosage” of other interventions received by the standard follow-up group or performed analysis in relation to services accessed by the follow-up group.

The amount of intervention received by infants and families in the treatment groups varied greatly between studies (from 4 - 336 sessions) and within studies. The relationship between intervention dosage and compliance with the intervention is important. Compliance may be estimated by attendance at designated visits or by therapists’ recordings of the impressions of compliance. The study by I.H.D.P. 1990 reported that higher levels of participation were related to better outcomes on the MDI and IQ scores at 24 and 36 months. In the study by Cameron 2005, a better motor outcome was reported at four months for the families with good compliance. However, subjective measurement of compliance by the study investigators may be biased and should be monitored independently.

There was a wide variety of measurement tools used in the studies, restricting the ability to pool data. There were fewer measurement tools utilized for assessing cognitive development than those used for assessing motor development, which made it possible to pool cognitive data for meta-analysis at different ages. The effect of early intervention on motor development could only be subjected to meta-analysis at infant age using the BSID-PDI or the Griffiths locomotor subscale and there was no treatment effect of intervention with either assessment. The BSID-PDI and Griffiths are broad measures of motor development and do not specifically evaluate minor motor problems, which are common in preterm infants. It is possible that these studies either have no effect on motor outcome or the measures were not sensitive enough to detect the effects of intervention on motor problems. Other motor measurement tools that assess movement quality and motor performance in more detail such as the AIMS, TIMP and Movement ABC were used by individual studies; however, it was not appropriate to pool these data for meta-analysis. The diversity of motor assessment tools and the lack of data at older ages limits the ability to compare results between studies. For example, the studies that relate to physical therapy all had different outcome measures. The meta-analysis of the long term effects of early developmental interventions on motor and cognitive outcome was limited not only by the small number of studies, but the low rates of follow up of these studies. The study by Nurcombe 1984 is the only study to report a treatment effect at school age; however, it is a relatively small study (n = 78) with only 71% children assessed at 9 years. The age of assessment of cognitive and motor outcomes may also be important. Interestingly, only five of the 11 studies that reported on cognitive outcome up to one year showed a significant effect favouring the intervention group. However, at two years, two studies that had previously shown no difference at 12 months
between treatment and control groups did have a significant effect favoring the intervention group. This may reflect the reliability and validity of the outcome measures at one year compared with two years, or that the effect of intervention is more apparent at two years.

The meta-analysis in this review has examined motor and cognitive outcomes using standardised assessments. In the past five years there has been a shift in how disability is measured. Instead of measuring disability using a medical framework, disability is measured using functional outcome, activity limitations and participation restrictions as part of a social and environmental framework (Simeonsson 2003). The World Health Organization now uses the International Classification of Functioning, Disability and Health rather than the old model of International Classification of Impairments, Disabilities and Handicaps (WHO 2001). It is possible that early intervention may not be able to change the physical outcome of a motor disorder, such as cerebral palsy; however, it may change how affected individuals function and participate in society. Intervention may affect motor outcome in a functional way. For example, the infant may be able to play outside on uneven surfaces, whereas without intervention the child may be restricted to indoor activities. Outcome measures such as the BSID-PDI and the Griffiths locomotor subscale measure global motor development in a controlled environment. The controlled environment where these assessments occur is often a quiet room set up for the infant or child to perform at their best. The skill level achieved in this setting may not be achievable in another setting, so it is important that their skills are assessed out of the testing situation and in their own specific environments. This review has only included traditional outcome measures of motor and cognitive outcome; however, as functional measures become more widely used it will be important to include these.

The methodological quality of the included studies was variable with only six of the 16 studies considered to be of high quality, that is being an RCT with a PEDro score greater than seven. Sensitivity analysis was performed to assess the effect of study quality on cognitive and motor outcomes. When only the higher quality studies were included in the meta-analysis there was still an intervention effect on cognitive outcome at infant and preschool age. There are some limitations to conducting intervention trials of developmental interventions. It is not feasible to mask the person implementing the intervention or the recipient of the intervention (in this case the mother and baby) unless a comparison group providing an alternative intervention is used instead of a control group. Only one study had a comparison treatment instead of a non-treatment control group (Melnyk 2001); however, this was not a randomised trial. When interventions are delivered, whether they focus on infant development or the parent-infant relationship, there is a component of parental support that may affect outcome. The study by APIP 1998 was the only study to control for parent support by having the three groups, one that received an infant development program, one that received parent support only, and a control group. The methodology quality assessments used in this review did not take sample size into account. Sample size is important when assessing the outcomes of individual programs since some studies may not have had enough power to demonstrate a difference between groups. The study by I.H.D.P. 1990 was by far the largest, with 985 infants included, followed by the study by APIP 1998 with 308 infants. The significant results of the I.H.D.P. 1990 and the large sample size influenced the overall results of the meta-analysis. The study by I.H.D.P. 1990 is very different from the other early developmental programs in frequency and duration of intervention, and this should be considered when interpreting the results of this review.

This systematic review has not investigated which aspects of early developmental interventions affect outcome more such as whether it is the optimal duration of intervention, the best age to begin the intervention, the optimal frequency, or the focus of intervention. Further research is needed to determine the components of intervention that are most effective based on cost and benefits. The I.H.D.P. 1990 was estimated to cost US$15,146 per year per child. The investigators suggest this value could be reduced to US$8806 if the centres were located in the community and teacher-child ratios were decreased. However, this is still a costly intervention compared with the study by Nurcombe 1984, which had better long term outcomes and would cost less to implement since there were only 11 sessions over four months compared with the intensive program over three years received by infants in the intervention group of the I.H.D.P. 1990 study.

**Authors’ Conclusions**

**Implications for practice**

Meta-analysis demonstrated that early developmental interventions post-hospital discharge for preterm infants have a significant impact on cognitive development at infant and preschool age. However, there is currently little evidence of an effect of early developmental interventions post-hospital discharge on motor development at infant age. At school age there have only been three studies that investigated the long term effects of intervention on cognitive outcome and two that investigated the effect on motor outcome, none of which demonstrated any substantial difference in long term outcomes. Interventions that focus on the parent-infant relationship, along with infant development, have the greatest impact on cognitive development in the short to medium term. The heterogeneity between early developmental intervention programs in regard to content, focus and intensity limit the conclusions that can be drawn from this review.

**Implications for research**

Further high quality randomised controlled trials are needed to...
identify the effective components of successful early development interventions for preterm infants. Greater selectivity of high risk populations may identify those infants who may benefit most from intervention. Targeting intervention to address the needs of the infant and family more specifically may reduce costs and increase effectiveness. Further research is also required on the effects of intervention programs on motor outcomes since only limited conclusions can be drawn from this review. There is a need for more high quality randomised controlled trials of intervention with long term follow up studies focusing on both motor and cognitive outcomes for preterm infants. Measurement tools need to be sensitive enough to detect change in motor performance and to identify minor neurological problems. This review has not investigated the effects on behaviour, parental outcomes (such as depression and anxiety), function, activity levels or participation, which may also be influenced by early developmental intervention programs.

ACKNOWLEDGEMENTS

Professor Jenny Keating, School of Primary Health Care, Monash University for her support and guidance at the commencement of this review.
Dr Klebenov for 12 and 24 month motor data from the IHDP.
Dr Ohgi for clarifying follow-up rates of participants.

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Barrera 1986 [published data only]
Cameron 2005 [published data only]

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I.H.D.P. 1990 [published and unpublished data]
Hollomon HA, Scott KG. Influence of birth weight on educational outcomes at age 9: the Miami site of the...


**Lekskulchai 2001 [published data only]**


**Melnyk 2001 [published data only]**


**Nelson 2001 [published data only]**


**Nurcombe 1984 [published data only]**


**Ohgi 2004 [published and unpublished data]**


**Piper 1986 [published data only]**


**Resnick 1979 [published data only]**


**Rice 1979 [published data only]**


**Yigit 2002 [published data only]**


References to studies excluded from this review

**Beckwith 1988 [published data only]**


**Beeghly 1995 [published data only]**


**Britain 1995 [published data only]**


**Chen 2001 [published data only]**


**Culp 1989 [published data only]**


**Girolami 1994 [published data only]**


**Israel 2003 [published data only]**

Early developmental intervention programs post hospital discharge to prevent motor and cognitive impairments in preterm infants

Kanda 2004 [published data only]

Kang 1995 [published data only]

Kendrick 2000 [published data only]

Kleberg 2000 [published data only]

Kleberg 2002 [published data only]

Matsuishi 1998 [published data only]

Ross 1984 [published data only]

Sajaniemi 2001 [published data only]

Salokorpi 2002 [published data only]

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Slater 1987 [published data only]

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Additional references

Als 1997

Anderson 2003

Bayley 1969

Bayley 1993

Becker 1999

Berger 1998

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Bruininks 1978

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Doyle 2004

Elliot 1996

Folio 2000

Griffiths 1954

Griffiths 1970

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Hadders-Algra 2001

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**Symington 2003**

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**Thelen 1996**

**Tin 1997**

**Verhagen 1998**

**Vohr 2000**

**Vohr 2005**

**Wang 2006**

**Wechsler 1989**

**Wechsler 1991**

**WHO 2001**

* Indicates the major publication for the study
**CHARACTERISTICS OF STUDIES**

**Characteristics of included studies [ordered by study ID]**

**APIP 1998**

| Methods | Blinding of intervention: no  
|         | Blinding of outcome assessments: yes  
|         | Completeness of follow-up: yes at 12 months* (86%)  
|         | Concealment of allocation: yes (opaque envelopes) |

| Participants | 309 infants  
|             | Inclusion criteria: GA <33 weeks  
|             | Exclusion criteria: English not first language and did not live within the study area  
|             | Characteristics: mean GA for the 2 treatment groups (Portage and Parent Advisor) and standard follow-up group was 31, 30 and 31 weeks respectively |

| Interventions | Two intervention programs were used, "Portage" and "Parent advisor" to control for the support aspect of Portage.  
|               | Portage group (n=111): infant development and parent support  
|               | Parent advisor group (n=99): parent support  
|               | For data analysis the Portage and parent advisor groups were included together as the intervention group.  
|               | Standard follow-up group (n=99): details of standard follow up for the control group are not reported |

| Outcomes | COGNITIVE:  
|          | - Infant age: Griffiths GCI (24 months)  
|          | - Preschool age: none  
|          | - School age: British Ability Scales 2nd Edition (5 years)  
|          | MOTOR  
|          | - Infant age: incidence of cerebral palsy  
|          | - Preschool age: none  
|          | - School age: Movement ABC (5 years) |

| Notes | The control group had a higher percentage of mothers who were educated beyond 16 years of age, were in non-manual occupations and had the use of a car compared with both intervention groups |

**Risk of bias**

<table>
<thead>
<tr>
<th>Item</th>
<th>Authors’ judgement</th>
<th>Description</th>
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<tbody>
<tr>
<td>Allocation concealment?</td>
<td>Yes</td>
<td>A - Adequate</td>
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### Bao 1999

<table>
<thead>
<tr>
<th><strong>Methods</strong></th>
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<tbody>
<tr>
<td>Blinding of intervention: no</td>
<td></td>
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<tr>
<td>Blinding of outcome assessments: yes</td>
<td></td>
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<tr>
<td>Completeness of follow-up: unclear as it is not stated if there were any infants who withdrew from the study</td>
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<tr>
<td>Concealment of allocation: the methods used to randomise the infants are not stated and therefore allocation concealment is unclear</td>
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<thead>
<tr>
<th><strong>Participants</strong></th>
<th>103 infants</th>
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<tbody>
<tr>
<td>Inclusion criteria: GA 28-37 weeks</td>
<td></td>
</tr>
<tr>
<td>Exclusion criteria: not reported</td>
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<tr>
<td>Characteristics: mean GA for the intervention and standard follow-up groups was 33.9 (SD 1.8) weeks and 34.2 (2.1) respectively</td>
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</table>

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<tr>
<th><strong>Interventions</strong></th>
<th>Intervention group (n=52): infant development</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Standard follow-up group (n=51): details are not described</td>
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<tr>
<th><strong>Outcomes</strong></th>
<th>COGNITIVE</th>
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<tbody>
<tr>
<td>Infant age: BSID-MDI-I (18 and 24 months)</td>
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</table>

| **MOTOR** | Infant age: BSID-PDI-I (18 and 24 months) |

### Barrera 1986

<table>
<thead>
<tr>
<th><strong>Methods</strong></th>
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<tbody>
<tr>
<td>Blinding of intervention: no</td>
<td></td>
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<tr>
<td>Blinding of outcome assessments: yes</td>
<td></td>
</tr>
<tr>
<td>Completeness of follow-up: no at 4, 8, 12 and 16 months (73%) and 5 years (56%)</td>
<td></td>
</tr>
<tr>
<td>Concealment of allocation: unclear (infants were block randomised according to sex, birth weight, socio-economic status and pre-/ post-natal complications, however, it is unclear what measures were taken to ensure concealment of allocation)</td>
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<table>
<thead>
<tr>
<th><strong>Participants</strong></th>
<th>80 infants</th>
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<tbody>
<tr>
<td>Inclusion criteria: BW &lt;2000 g or GA &lt; = 37 weeks and discharged home from hospital with a good prognosis for survival</td>
<td></td>
</tr>
<tr>
<td>Exclusion criteria: life threatening illnesses or did not live within the study area</td>
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<tr>
<td>Characteristics: The mean GA for all groups was 33 weeks</td>
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<table>
<thead>
<tr>
<th><strong>Interventions</strong></th>
<th>Two intervention programs were compared to standard follow-up.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Parent-infant intervention (n=22*): parent-infant relationship</td>
<td></td>
</tr>
<tr>
<td>Developmental programme (n=16*): infant development</td>
<td></td>
</tr>
<tr>
<td>For data analysis the two parent-infant and developmental groups were included together as the intervention group.</td>
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**Risk of bias**

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<th><strong>Item</strong></th>
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<tr>
<td>Allocation concealment?</td>
<td>No</td>
<td>C - Inadequate</td>
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</table>
Barrera 1986  (Continued)

| Outcomes | COGNITIVE  
|          | - Infant age: BSID-MDI-I (4, 8, 12 and 16 months)  
|          | - Preschool age: McCarthy Scales of Children's Abilities - general cognitive index (4.5-5 years)  
|          | MOTOR  
|          | - Infant age: BSID-PDI-I (4, 8, 12 and 16 months)  
| Notes | *Twenty-one infants did not complete the study. The number of infants in each group listed is for infants who completed the 1-year program, as the number of infants randomised to each group at the beginning of the study is not stated. It is reported that there was no differences in reasons for withdrawing from the study between groups  

### Risk of bias

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<td>Allocation concealment?</td>
<td>Unclear</td>
<td>B - Unclear</td>
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Cameron 2005

| Methods | Blinding of intervention: no  
|         | Blinding of outcome assessments: yes  
|         | Completeness of follow-up: no at 4 months (83%)  
|         | Concealment of allocation: adequate (toss of coin)  
| Participants | 72 infants  
|              | Inclusion criteria: BW <1500 g and GA<32 weeks  
|              | Exclusion criteria: required oxygen at 4 months corrected age, severe hydrocephalus requiring a shunt, demonstrated signs of drug withdrawal or with history of social problems  
|              | Characteristics: mean GA for the treatment and standard follow-up groups was 28.7 (SD = 2.4) and 29.6 (SD = 2.0) respectively  
| Interventions | Intervention group (n=34): infant development  
|              | Standard follow-up group (n = 38): no physiotherapy intervention or other placebo intervention was given  
| Outcomes | COGNITIVE  
|          | - none  
|          | MOTOR  
|          | -Infant age: Alberta Infant Motor Scale (4 months) and incidence of cerebral palsy (18 months)  

Notes

### Risk of bias

<table>
<thead>
<tr>
<th>Item</th>
<th>Authors’ judgement</th>
<th>Description</th>
</tr>
</thead>
</table>

Early developmental intervention programs post hospital discharge to prevent motor and cognitive impairments in preterm infants (Review)  
Copyright © 2009 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.
### Cameron 2005

#### Allocation concealment?

| Yes | A - Adequate |

### Field 1980

<table>
<thead>
<tr>
<th>Methods</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blinding of intervention: no</td>
</tr>
<tr>
<td>Blinding of outcome assessments: yes</td>
</tr>
<tr>
<td>Completeness of follow-up: yes at 8 months (85.5%)</td>
</tr>
<tr>
<td>Concealment of allocation: unclear</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Participants</th>
</tr>
</thead>
<tbody>
<tr>
<td>60 infants</td>
</tr>
<tr>
<td>Inclusion criteria: BW &lt;2500 g and GA&lt;37. All infants were born to African American teenage mothers with low socio-demographic status.</td>
</tr>
<tr>
<td>Exclusion criteria: serious neonatal complications that would require long periods of intensive care and early separation</td>
</tr>
<tr>
<td>Characteristics: mean GA of the intervention and standard follow-up groups was 35.5 and 35.3 weeks respectively</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Interventions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intervention group (n=30): infant development and parent-infant relationship</td>
</tr>
<tr>
<td>Standard follow up (n=30): no details on standard follow up are given</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>COGNITIVE</td>
</tr>
<tr>
<td>- Infant age: BSID-I MDI (8 months)</td>
</tr>
<tr>
<td>MOTOR</td>
</tr>
<tr>
<td>- Infant age: BSID-I PDI (8 months)</td>
</tr>
</tbody>
</table>

### Goodman 1985

<table>
<thead>
<tr>
<th>Methods</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blinding of intervention: no</td>
</tr>
<tr>
<td>Blinding of outcome assessments: yes</td>
</tr>
<tr>
<td>Completeness of follow-up: no at 12 months (75%) and 6 years (61%)</td>
</tr>
<tr>
<td>Concealment of allocation: inadequate (infants were alternatively allocated to treatment or control groups)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Participants</th>
</tr>
</thead>
<tbody>
<tr>
<td>107 infants*</td>
</tr>
<tr>
<td>Inclusion criteria: BW &lt;1700 g or GA &lt;34 weeks.</td>
</tr>
<tr>
<td>Exclusion criteria: infants who were considered as neurologically impaired were excluded from the study as they were all given intervention.</td>
</tr>
<tr>
<td>Characteristics: mean GA of the intervention and standard follow-up groups was 30.9 (SD =1.9) and 31 (SD = 1.8) respectively</td>
</tr>
</tbody>
</table>
Interventions

Intervention group (n=40): infant development
Standard follow-up group (n=40): infants in both groups (intervention and standard follow-up) attended a follow-up clinic at 6 weeks, 3, 6, 9 and 12 months’ corrected age. This clinic was staffed by a neonatologist, physiotherapists, speech and hearing therapist, ophthalmologists, public health nurses and social workers. It is not clear how much “intervention” was provided to infants in the control group during these visits.

Outcomes

COGNITIVE
- Infant age: Griffiths Mental Development Scale (12 months)
- School age: Griffiths Mental Development Scale 2 (6 years)

MOTOR
- Infant age: the Griffiths Developmental Quotient (locomotor sub scale) (12 months)
- School age: the Griffiths Development Quotient (locomotor sub scale), neurological examination to assess the incidence of cerebral palsy and clumsiness/coordination problems (6 years)

Notes

* Prior to commencing study the authors stated that intention was to study 40 infants in each group. To allow for attrition, 107 infants were enrolled in the study at 3 months. However, the formal study ceased when 80 infants were followed up to 3 months.

Risk of bias

<table>
<thead>
<tr>
<th>Item</th>
<th>Authors’ judgement</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Allocation concealment?</td>
<td>No</td>
<td>C - Inadequate</td>
</tr>
</tbody>
</table>

I.H.D.P. 1990

Methods

Blinding of intervention: no
Blinding of outcome assessments: yes
Completeness of follow-up: yes at 12 months (90%), 24 month (89%), 36 month (93%) and 8 years (89%), however, not at 5 years (82%)
Concealment of allocation: adequate (adaptive randomisation method)

Participants

985 infants
Inclusion criteria: BW =<2500 g or GA < 37 weeks
Exclusion criteria: congenital abnormalities, genetic disorders still hospitalised or too sick to participate in the program at term
Characteristics: mean GA for the intervention and standard follow-up groups was 33 weeks

Interventions

Intervention group (n=377): infant development and parent-infant relationship
Standard follow-up group (n=608): both groups received medical, developmental and social assessments, with referral to other services as indicated

Outcomes

COGNITIVE
- Infant age: BSID-I MDI (12 and 24 months)
- Preschool age: Stanford-Binet Intelligence Scale (36 months)
- School age: WPPSI (5 years) and WISC-III (8 years)

MOTOR
- Infant age: BSID-I PDI (12 and 24 months)
### Notes
Additional data (means and SD for 12 and 24 months for MDI and PDI) were obtained from authors for meta-analysis.

### Risk of bias

<table>
<thead>
<tr>
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<th>Authors’ judgement</th>
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</tr>
</thead>
<tbody>
<tr>
<td>Allocation concealment?</td>
<td>Yes</td>
<td>A - Adequate</td>
</tr>
</tbody>
</table>

#### Lekskulchai 2001

**Methods**
- Blinding of intervention: no
- Blinding of outcome assessments: yes
- Completeness of follow-up: yes at 1, 2, 3 and 4 months (86%)
- Concealment of allocation: adequate (intervention or control slip was taken blindly from a container)

**Participants**
- 84 infants
- Inclusion criteria: BW GA<37 weeks considered to be “at-risk” of adverse neurological sequelae assessed with the TIMP at 40 weeks post conceptional age.
- Exclusion criteria: congenital abnormalities, genetic disorders, surgery or developed serious illness including hydrocephalus and periventricular haemorrhage (grade III) were excluded prior to randomisation.
- Characteristics: mean GA for the intervention and standard follow-up group was 31.9 (SD=2.4) and 32.3 (SD=2.2) weeks respectively

**Interventions**
- Intervention group (n=43): infant development
- Standard follow-up (n=41): all families (intervention and standard follow-up) were assessed (using the TIMP) by a research assistant 1, 2, 3 and 4 months and were able to discuss any concerns with principal researcher

**Outcomes**
- COGNITIVE
  - None
- MOTOR
  - Infant age: Test of Infant Motor Performance (1, 2, 3 and 4 months)

**Notes**
Unable to use data in meta-analysis as the outcome measure (TIMP) was not appropriate to pool with other outcome measures.

### Risk of bias

<table>
<thead>
<tr>
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</tr>
</thead>
<tbody>
<tr>
<td>Allocation concealment?</td>
<td>Yes</td>
<td>A - Adequate</td>
</tr>
</tbody>
</table>
### Melnyk 2001

| Methods              | Blinding of intervention: yes  
|                      | Blinding of outcome assessments: yes  
|                      | Completeness of follow-up: no at 3 and 6 months (76%)  
|                      | Concealment of allocation: inadequate (infants were randomised according to date admitted to hospital)  
| Participants         | 55 infants  
|                      | Inclusion criteria: BW <2000 g and GA <34 weeks  
|                      | Exclusion criteria: perinatal hypoxia or abnormal ultra-sound, with no congenital or chromosomal abnormalities or metabolic disease  
|                      | Characteristics: mean GA for the intervention group and standard follow-up groups was 31.3 (SD=2.2) and 32.0 (SD=1.6) weeks respectively  
| Interventions        | Intervention group (n=26): parent-infant relationship  
|                      | Standard follow-up group (n=29): received a placebo intervention which also consisted of audio-taped and written information in relation to hospital services, routine discharge information and education about immunisations  
| Outcomes             | COGNITIVE  
|                      | - Infant age: Bayley Scales of Infant Development-MDI II (3 and 6 months)  
|                      | MOTOR  
|                      | - None  
| Notes                | This was the only study to have a comparison group who received a placebo intervention  

#### Risk of bias

| Item                              | Authors’ judgement | Description  
|-----------------------------------|--------------------|--------------  
| Allocation concealment?           | No                 | C - Inadequate  

### Nelson 2001

| Methods              | Blinding of intervention: no  
|                      | Blinding of outcome assessments: yes  
|                      | Completeness of follow-up: no at 12 months (70%)  
|                      | Concealment of allocation: unclear  
| Participants         | 37 infants  
|                      | Inclusion criteria: BW <1500 g and GA 23-26 weeks (group 1) or born between 23-32 weeks and diagnosed with PVL or grade III IVH (group 2)  
|                      | Exclusion criteria: not medically stable, required mechanical ventilation or not feeding at the commencement of the study (intervention commenced while the infants were in the NICU), intra-uterine growth restriction, chromosome disorders and necrotizing enterocolitis.  
|                      | Characteristics: mean GA for the intervention and control groups for group 1 was 25.6 (SD=1.1) and 25.6 (SD=1.5) and for group 2 was 27.2 (SD=2.9) and 27.3 (SD=2.4) weeks respectively  
| Interventions        | The intervention group (n=21): infant development and parent-infant relationship  
|                      | Standard follow-up (n=16): all infants (intervention and standard follow-up groups) received developmental care
Nelson 2001  (Continued)

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>COGNITIVE</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>- Infant age: BSID-II MDI (12 months)</td>
</tr>
<tr>
<td>MOTOR</td>
<td>- Infant age: BSID-II PDI (12 months)</td>
</tr>
</tbody>
</table>

<table>
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<tr>
<th>Notes</th>
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**Risk of bias**

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<tr>
<th>Item</th>
<th>Authors’ judgement</th>
<th>Description</th>
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</thead>
<tbody>
<tr>
<td>Allocation concealment?</td>
<td>Unclear</td>
<td>B - Unclear</td>
</tr>
</tbody>
</table>

Nurcombe 1984

| Methods | Blinding of intervention: no  
|         | Blinding of outcome assessments: yes  
|         | Completeness of follow-up: yes at 12 months (95%), however, longer term follow up was not adequate at 24, 36 and 48 months (68%) and at 7 and 9 years (71%).  
|         | Concealment of allocation: adequate (infants were randomised by toss of coin, ensuring allocation concealment) |

| Participants | 78 infants  
|             | Inclusion criteria: BW <2250 g and GA <37 weeks  
|             | Exclusion criteria: congenital abnormalities, severe neurological defects, multiple births and single mothers  
|             | Characteristics: mean GA for the treatment and standard follow-up groups was 32.3 (SD=2.4) and 31.9 (SD=2.4) weeks respectively. There was a significant difference in the SES of the intervention and standard follow-up groups despite randomisation |

| Interventions | Intervention group (n=38): infant development and parent-infant relationship  
|               | Standard follow-up (n=40): no details of the standard follow-up are reported |

| Outcomes | COGNITIVE  
|----------|------------|
|          | Infant age: BSID-I MDI (6, 12 and 24 months)  
|         | Preschool age: McCarthy Scales (3 and 4 years)  
|         | School age: Kaufman Assessment Battery for Children (7 and 9 years)  
| MOTOR   | Infant age: BSID-I PDI (6, 12 and 24 months) |

| Notes | Reported data has been adjusted to control for socio-economic status of families |

**Risk of bias**

<table>
<thead>
<tr>
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<tbody>
<tr>
<td>Allocation concealment?</td>
<td>Yes</td>
<td>A - Adequate</td>
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<tr>
<td>------------------------</td>
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<td>-------------</td>
</tr>
</tbody>
</table>

**Nurcombe 1984** *(Continued)*

**Ohgi 2004**

**Methods**
- Blinding of intervention: no
- Blinding of outcome assessments: yes
- Completeness of follow-up: yes at 12 months (96%)
- Concealment of allocation: yes (method of minimisation)

**Participants**
- 24 infants
- Inclusion criteria: BW <2500 g who were at high-risk of neurological problems due to PVL and/or IVH (as shown by ultrasound)
- Exclusion criteria: multiple births, born in another town and returned there
- Characteristics: Mean GA for treatment and followup groups were 30.3(SD=3.3) and 30.3(SD=2.7) weeks respectively. There were no significant differences between groups for infant and maternal factors, social factors, distribution of diagnoses and severity of injury

**Interventions**
- The intervention group (n=12): infant developmental and parent-infant relationship
- Standard follow-up (n=12): all infants in the control and intervention groups attended follow up clinics and were referred to developmental services if infants presented with signs of neurological dysfunction or developmental delay

**Outcomes**
- COGNITIVE
  - Infant age: BSID-II MDI (6 months)
- MOTOR
  - Infant age: BSID-II PDI (6 months)

**Notes**

**Risk of bias**

<table>
<thead>
<tr>
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</thead>
<tbody>
<tr>
<td>Allocation concealment?</td>
<td>Yes</td>
<td>A - Adequate</td>
</tr>
</tbody>
</table>

**Piper 1986**

**Methods**
- Multi centre randomised trial
- Blinding of intervention: no
- Blinding of outcome assessments: yes
- Completeness of follow-up: yes at 12 months* (86%)
- Concealment of allocation: yes (opaque envelopes)

**Participants**
- 134 infants (115 LBW infants)
- Inclusion criteria: BW <1500 g (group 1) or birth asphyxia and seizures regardless of GA (group 2).
- Characteristics: mean GA for the intervention and control groups was 29.9 (SD=3.8) and 29.3 (SD=3.7) weeks respectively
Interventions

- Intervention group (n=56): infant development
- Standard follow-up (n=59): all infants attended neonatal follow-up programs and infants in the standard follow-up group could be referred to physiotherapy at any time if indicated by their paediatrician. Seven control infants received physical therapy intervention after 6 months of age.

Outcomes

- COGNITIVE
  - The Griffiths Mental Development Scale (12 months)
- MOTOR

Notes

- The study involved a group of preterm infants and a group of infants at risk of neurological sequelae. There was adequate follow up of the whole cohort at 12 months with 86% of infants seen, however, the follow up rates of the preterm infant group alone are not stated.
- Not used in meta-analysis as standard deviations are not reported and population includes infants who were not born preterm.

Risk of bias

<table>
<thead>
<tr>
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<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Allocation concealment?</td>
<td>Yes</td>
<td>A - Adequate</td>
</tr>
</tbody>
</table>

Resnick 1988

Methods

- Blinding of intervention: no
- Blinding of outcome assessments: yes
- Completeness of follow-up: unclear as it is not stated whether there was any subjects who exited the study prior to the 12 month assessment
- Concealment of allocation: inadequate (infants were randomised according to the last digit of hospital number)

Participants

- 41 infants
- Inclusion criteria: BW<1800 g, GA < 37 weeks
- Exclusion criteria: not specified
- Characteristics: mean GA for the intervention group and control groups was 31.7 (SD=2.9) and 31.0 (SD=2.0) weeks respectively

Interventions

- Intervention group (n=21): infant development and parent-infant relationship
- Standard follow-up group (n=20): received access to a full range of social services, physiotherapy and occupational therapy

Outcomes

- COGNITIVE
  - Infant age: Bayley Scales of Infant Development-I MDI (6 and 12 months)
- MOTOR
  - Infant age: Bayley Scales of Infant Development-I PDI (6 and 12 months)
### Rice 1979

**Methods**
- Blinding of intervention: no
- Blinding of outcome assessments: yes
- Completeness of follow-up: unclear (it is not stated if there was any infants who withdrew from the study)
- Concealment of allocation: unclear

**Participants**
- 30 infants
- Inclusion criteria: born at GA <37 weeks between 1974 and 1975 born to mothers of low socioeconomic status.
- Exclusion criteria: not specified
- Characteristics: mean GA for the intervention and control group is not stated but reported to be similar between control and intervention groups

**Interventions**
- Intervention group (n=15): infant development
- Standard follow-up (n=15): mothers were given standard discharge information related to caring for their infant. It is reported that mothers were visited regularly by the experimenter and by other public health nurses to provide social reinforcement for appropriate mothering behavior

**Outcomes**
- COGNITIVE
  - Infant age: BSID-I MDI (4 months)
- MOTOR
  - Infant age: BSID-I PDI (4 months)

### Risk of bias

<table>
<thead>
<tr>
<th>Item</th>
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<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
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<td>C - Inadequate</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
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<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Allocation concealment?</td>
<td>Unclear</td>
<td>B - Unclear</td>
</tr>
</tbody>
</table>

**Notes**
- Allocation concealment?
  - No, C - Inadequate
### Methods

- Blinding of intervention: no
- Blinding of outcome assessments: unclear
- Completeness of follow-up: no (83% follow up at 12 months)
- Concealment of allocation: unclear

### Participants

- 199 infants*
- Inclusion criteria: BW <2000 g and GA <34 weeks
- Exclusion criteria: perinatal hypoxia or abnormal ultrasound, with no congenital or chromosomal abnormalities or metabolic disease
- The mean GA for the intervention group and standard follow-up groups was 31.3 (SD=2.2) and 32.0 (SD=1.6) weeks respectively

### Interventions

- The intervention group (n=80): infant development
- The standard follow-up group (n=80): both groups seen monthly by the same physiotherapist for the first 9 months, then every 3 months until 18-24 months of age. It is unclear whether this was for assessment or intervention

### Outcomes

- **COGNITIVE**
  - None
- **MOTOR**
  - Infant age only: Non-standardised measures of motor outcome such as age of acquisition of milestones and loss of primitive reflexes (1 month - 18-24 months). Incidence of cerebral palsy

### Notes

- *It is stated that 39 infants dropped out of the study due to lack of participation at 12 months, however, the number of infants initially randomised to intervention and standard follow-up is not reported
- Data not able to be used in meta-analysis as it is not standardised

### Risk of bias

<table>
<thead>
<tr>
<th>Item</th>
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</tr>
</thead>
<tbody>
<tr>
<td>Allocation concealment?</td>
<td>Unclear</td>
<td>B - Unclear</td>
</tr>
</tbody>
</table>

### Characteristics of excluded studies  [ordered by study ID]

<table>
<thead>
<tr>
<th>Study</th>
<th>Reason for exclusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Beckwith 1988</td>
<td>Intervention: no post-hospital discharge component</td>
</tr>
<tr>
<td>Beeghly 1995</td>
<td>Population: infants not preterm</td>
</tr>
<tr>
<td>Britain 1995</td>
<td>Methodology: case studies</td>
</tr>
<tr>
<td>Chen 2001</td>
<td>Language: published in Chinese</td>
</tr>
<tr>
<td>Culp 1989</td>
<td>Outcome measures: parent focused only</td>
</tr>
<tr>
<td>Reference</td>
<td>Intervention</td>
</tr>
<tr>
<td>----------------</td>
<td>------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Girolami 1994</td>
<td>Intervention: no post-hospital discharge component</td>
</tr>
<tr>
<td>Israel 2003</td>
<td></td>
</tr>
<tr>
<td>Kanda 2004</td>
<td>Methodology: case-control study</td>
</tr>
<tr>
<td>Kang 1995</td>
<td></td>
</tr>
<tr>
<td>Kendrick 2000</td>
<td>Methodology: literature review only</td>
</tr>
<tr>
<td>Kleberg 2000</td>
<td>Intervention: no post-hospital discharge component</td>
</tr>
<tr>
<td>Kleberg 2002</td>
<td>Intervention: no post-hospital discharge component</td>
</tr>
<tr>
<td>Matsuishi 1998</td>
<td>Methodology: case-control study</td>
</tr>
<tr>
<td>Ross 1984</td>
<td>Methodology: case-control study</td>
</tr>
<tr>
<td>Sajaniemi 2001</td>
<td>Methodology: case-control study</td>
</tr>
<tr>
<td>Salokorpi 2002</td>
<td>Methodology: case-control study</td>
</tr>
<tr>
<td>Scott 1989</td>
<td>Methodology: literature review only</td>
</tr>
<tr>
<td>Slater 1987</td>
<td>Methodology: cohort study</td>
</tr>
<tr>
<td>Wasik 1990</td>
<td>Population: infants are not preterm</td>
</tr>
</tbody>
</table>

Early developmental intervention programs post hospital discharge to prevent motor and cognitive impairments in preterm infants (Review)

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## DATA AND ANALYSES

### Comparison 1. Early developmental intervention vs standard follow-up (all studies)

<table>
<thead>
<tr>
<th>Outcome or subgroup title</th>
<th>No. of studies</th>
<th>No. of participants</th>
<th>Statistical method</th>
<th>Effect size</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 Cognitive outcome at infant age - DQ (BSID-MDI, Griffiths GCI)</td>
<td>8</td>
<td>1444</td>
<td>Std. Mean Difference (IV, Fixed, 95% CI)</td>
<td>0.46 [0.36, 0.57]</td>
</tr>
<tr>
<td>2 Cognitive outcome at preschool age - IQ (Stanford Binet, McCarthy)</td>
<td>3</td>
<td>1006</td>
<td>Std. Mean Difference (IV, Fixed, 95% CI)</td>
<td>0.46 [0.33, 0.59]</td>
</tr>
<tr>
<td>3 Cognitive outcome at school age - IQ (WISC, Kaufmann)</td>
<td>3</td>
<td>1111</td>
<td>Std. Mean Difference (IV, Fixed, 95% CI)</td>
<td>0.02 [-0.10, 0.14]</td>
</tr>
<tr>
<td>4 Motor outcome at infant age (BSID PDI, Griffiths locomotor)</td>
<td>6</td>
<td>1149</td>
<td>Std. Mean Difference (IV, Fixed, 95% CI)</td>
<td>0.05 [-0.06, 0.17]</td>
</tr>
<tr>
<td>5 Motor outcome at pre-school age (Griffiths locomotor)</td>
<td>0</td>
<td>0</td>
<td>Std. Mean Difference (IV, Fixed, 95% CI)</td>
<td>Not estimable</td>
</tr>
<tr>
<td>6 Motor outcome at school age (Low score on Movement-ABC)</td>
<td>1</td>
<td>49</td>
<td>Std. Mean Difference (IV, Fixed, 95% CI)</td>
<td>-0.34 [-0.91, 0.23]</td>
</tr>
<tr>
<td>7 Motor outcome at school age (Low score on Movement-ABC)</td>
<td>1</td>
<td>197</td>
<td>Risk Ratio (M-H, Fixed, 95% CI)</td>
<td>1.04 [0.78, 1.38]</td>
</tr>
<tr>
<td>8 Rate of cerebral palsy</td>
<td>4</td>
<td>586</td>
<td>Risk Ratio (M-H, Fixed, 95% CI)</td>
<td>0.95 [0.57, 1.58]</td>
</tr>
</tbody>
</table>

### Comparison 2. Early developmental intervention vs standard follow-up (subgroup analysis: gestational age)

<table>
<thead>
<tr>
<th>Outcome or subgroup title</th>
<th>No. of studies</th>
<th>No. of participants</th>
<th>Statistical method</th>
<th>Effect size</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 Cognitive outcome at infant age DQ (BSID-MDI, Griffiths GCI)</td>
<td>1</td>
<td></td>
<td>Std. Mean Difference (IV, Fixed, 95% CI)</td>
<td>Subtotals only</td>
</tr>
<tr>
<td>1.1 Preterm</td>
<td>0</td>
<td>0</td>
<td>Std. Mean Difference (IV, Fixed, 95% CI)</td>
<td>Not estimable</td>
</tr>
<tr>
<td>1.2 Very preterm</td>
<td>1</td>
<td>153</td>
<td>Std. Mean Difference (IV, Fixed, 95% CI)</td>
<td>0.09 [-0.25, 0.43]</td>
</tr>
<tr>
<td>1.3 Extremely preterm</td>
<td>1</td>
<td>87</td>
<td>Std. Mean Difference (IV, Fixed, 95% CI)</td>
<td>0.39 [-0.06, 0.83]</td>
</tr>
</tbody>
</table>
### Comparison 3. Early developmental intervention vs standard follow-up (subgroup analysis: birthweight)

<table>
<thead>
<tr>
<th>Outcome or subgroup title</th>
<th>No. of studies</th>
<th>No. of participants</th>
<th>Statistical method</th>
<th>Effect size</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 Cognitive outcome at infant age - DQ (BSID- MDI, Griffiths GCI)</td>
<td>1</td>
<td>322</td>
<td>Std. Mean Difference (IV, Fixed, 95% CI)</td>
<td>Subtotals only</td>
</tr>
<tr>
<td>1.1 Low birth weight</td>
<td>1</td>
<td>322</td>
<td>Std. Mean Difference (IV, Fixed, 95% CI)</td>
<td>0.75 [0.52, 0.98]</td>
</tr>
<tr>
<td>1.2 Very low birth weight</td>
<td>0</td>
<td>0</td>
<td>Std. Mean Difference (IV, Fixed, 95% CI)</td>
<td>Not estimable</td>
</tr>
<tr>
<td>1.3 Extremely low birth weight</td>
<td>0</td>
<td>0</td>
<td>Std. Mean Difference (IV, Fixed, 95% CI)</td>
<td>Not estimable</td>
</tr>
<tr>
<td>2 Cognitive outcome at pre-school age - IQ(Stanford Binet, McCarthy)</td>
<td>1</td>
<td>328</td>
<td>Std. Mean Difference (IV, Fixed, 95% CI)</td>
<td>Subtotals only</td>
</tr>
<tr>
<td>2.1 Low birth weight</td>
<td>1</td>
<td>328</td>
<td>Std. Mean Difference (IV, Fixed, 95% CI)</td>
<td>0.70 [0.47, 0.93]</td>
</tr>
<tr>
<td>2.2 Very low birth weight</td>
<td>0</td>
<td>0</td>
<td>Std. Mean Difference (IV, Fixed, 95% CI)</td>
<td>Not estimable</td>
</tr>
<tr>
<td>2.3 Extremely low birth weight</td>
<td>0</td>
<td>0</td>
<td>Std. Mean Difference (IV, Fixed, 95% CI)</td>
<td>Not estimable</td>
</tr>
</tbody>
</table>

### Comparison 4. Early developmental intervention vs standard follow-up (subgroup analysis: brain injury)

<table>
<thead>
<tr>
<th>Outcome or subgroup title</th>
<th>No. of studies</th>
<th>No. of participants</th>
<th>Statistical method</th>
<th>Effect size</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 Cognitive outcome at infant age - DQ (BSID- MDI, Griffiths GCI)</td>
<td>2</td>
<td></td>
<td>Std. Mean Difference (IV, Fixed, 95% CI)</td>
<td>Subtotals only</td>
</tr>
<tr>
<td>1.1 Absence of PVL/IVH</td>
<td>0</td>
<td>0</td>
<td>Std. Mean Difference (IV, Fixed, 95% CI)</td>
<td>Not estimable</td>
</tr>
<tr>
<td>1.2 Presence of PVL/IVH</td>
<td>2</td>
<td>41</td>
<td>Std. Mean Difference (IV, Fixed, 95% CI)</td>
<td>0.50 [-0.12, 1.13]</td>
</tr>
<tr>
<td>2 Motor outcome at infant age (BSID PDI, Griffiths locomotor)</td>
<td>2</td>
<td></td>
<td>Std. Mean Difference (IV, Fixed, 95% CI)</td>
<td>Subtotals only</td>
</tr>
<tr>
<td>2.1 Absence of PVL/IVH</td>
<td>0</td>
<td>0</td>
<td>Std. Mean Difference (IV, Fixed, 95% CI)</td>
<td>Not estimable</td>
</tr>
<tr>
<td>2.2 Presence of PVL/IVH</td>
<td>2</td>
<td>41</td>
<td>Std. Mean Difference (IV, Fixed, 95% CI)</td>
<td>0.47 [-0.15, 1.10]</td>
</tr>
</tbody>
</table>
### Comparison 5. Early developmental intervention vs standard follow-up (subgroup analysis: commencement of intervention)

<table>
<thead>
<tr>
<th>Outcome or subgroup title</th>
<th>No. of studies</th>
<th>No. of participants</th>
<th>Statistical method</th>
<th>Effect size</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 Cognitive outcome at infant age - DQ (BSID- MDI, Griffiths GCI)</td>
<td>8</td>
<td></td>
<td>Std. Mean Difference (IV, Fixed, 95% CI)</td>
<td>Subtotals only</td>
</tr>
<tr>
<td>1.1 In-patient</td>
<td>4</td>
<td>145</td>
<td>Std. Mean Difference (IV, Fixed, 95% CI)</td>
<td>0.55 [0.22, 0.89]</td>
</tr>
<tr>
<td>1.2 Post hospital discharge</td>
<td>4</td>
<td>1299</td>
<td>Std. Mean Difference (IV, Fixed, 95% CI)</td>
<td>0.45 [0.34, 0.57]</td>
</tr>
<tr>
<td>2 Cognitive outcome at pre-school age - IQ (Stanford Binet, McCarthy)</td>
<td>3</td>
<td></td>
<td>Std. Mean Difference (IV, Fixed, 95% CI)</td>
<td>Subtotals only</td>
</tr>
<tr>
<td>2.1 In-patient</td>
<td>1</td>
<td>53</td>
<td>Std. Mean Difference (IV, Fixed, 95% CI)</td>
<td>0.79 [0.23, 1.35]</td>
</tr>
<tr>
<td>2.2 Post hospital discharge</td>
<td>2</td>
<td>953</td>
<td>Std. Mean Difference (IV, Fixed, 95% CI)</td>
<td>0.44 [0.31, 0.57]</td>
</tr>
<tr>
<td>3 Cognitive outcome at school age - IQ (WISC, Kaufmann)</td>
<td>3</td>
<td></td>
<td>Std. Mean Difference (IV, Fixed, 95% CI)</td>
<td>Subtotals only</td>
</tr>
<tr>
<td>3.1 In-patient</td>
<td>1</td>
<td>55</td>
<td>Std. Mean Difference (IV, Fixed, 95% CI)</td>
<td>1.02 [0.45, 1.59]</td>
</tr>
<tr>
<td>3.2 Post hospital discharge</td>
<td>2</td>
<td>1056</td>
<td>Std. Mean Difference (IV, Fixed, 95% CI)</td>
<td>-0.02 [-0.15, 0.10]</td>
</tr>
<tr>
<td>4 Motor outcome at infant age (BSID PDI, Griffiths locomotor)</td>
<td>6</td>
<td></td>
<td>Std. Mean Difference (IV, Fixed, 95% CI)</td>
<td>Subtotals only</td>
</tr>
<tr>
<td>4.1 In-patient</td>
<td>3</td>
<td>120</td>
<td>Std. Mean Difference (IV, Fixed, 95% CI)</td>
<td>-0.03 [-0.39, 0.33]</td>
</tr>
<tr>
<td>4.2 Post hospital discharge</td>
<td>3</td>
<td>1029</td>
<td>Std. Mean Difference (IV, Fixed, 95% CI)</td>
<td>0.06 [-0.06, 0.19]</td>
</tr>
<tr>
<td>5 Motor outcome at pre-school age (Griffiths locomotor)</td>
<td>0</td>
<td></td>
<td>Std. Mean Difference (IV, Fixed, 95% CI)</td>
<td>Subtotals only</td>
</tr>
<tr>
<td>5.1 In-patient</td>
<td>0</td>
<td>0</td>
<td>Std. Mean Difference (IV, Fixed, 95% CI)</td>
<td>Not estimable</td>
</tr>
<tr>
<td>5.2 Post hospital discharge</td>
<td>0</td>
<td>0</td>
<td>Std. Mean Difference (IV, Fixed, 95% CI)</td>
<td>Not estimable</td>
</tr>
<tr>
<td>6 Motor outcome at school age (Low score on Movement-ABC)</td>
<td>1</td>
<td></td>
<td>Std. Mean Difference (IV, Fixed, 95% CI)</td>
<td>Subtotals only</td>
</tr>
<tr>
<td>6.1 In-patient</td>
<td>0</td>
<td>0</td>
<td>Std. Mean Difference (IV, Fixed, 95% CI)</td>
<td>Not estimable</td>
</tr>
<tr>
<td>6.2 Post hospital discharge</td>
<td>1</td>
<td>49</td>
<td>Std. Mean Difference (IV, Fixed, 95% CI)</td>
<td>-0.34 [-0.91, 0.23]</td>
</tr>
<tr>
<td>7 Rate of cerebral palsy</td>
<td>4</td>
<td></td>
<td>Risk Ratio (M-H, Fixed, 95% CI)</td>
<td>Subtotals only</td>
</tr>
<tr>
<td>7.1 In-patient</td>
<td>1</td>
<td>197</td>
<td>Risk Ratio (M-H, Fixed, 95% CI)</td>
<td>Not estimable</td>
</tr>
<tr>
<td>7.2 Post hospital discharge</td>
<td>1</td>
<td>60</td>
<td>Risk Ratio (M-H, Fixed, 95% CI)</td>
<td>1.04 [0.78, 1.38]</td>
</tr>
<tr>
<td>8 Rate of cerebral palsy</td>
<td>4</td>
<td></td>
<td>Risk Ratio (M-H, Fixed, 95% CI)</td>
<td>Subtotals only</td>
</tr>
<tr>
<td>8.1 In-patient</td>
<td>1</td>
<td>60</td>
<td>Risk Ratio (M-H, Fixed, 95% CI)</td>
<td>2.29 [0.77, 6.78]</td>
</tr>
<tr>
<td>8.2 Post hospital discharge</td>
<td>3</td>
<td>526</td>
<td>Risk Ratio (M-H, Fixed, 95% CI)</td>
<td>0.73 [0.40, 1.32]</td>
</tr>
</tbody>
</table>
### Comparison 6. Early developmental intervention vs standard follow-up (subgroup analysis: focus of intervention)

<table>
<thead>
<tr>
<th>Outcome or subgroup title</th>
<th>No. of studies</th>
<th>No. of participants</th>
<th>Statistical method</th>
<th>Effect size</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 Cognitive outcome at infant age</td>
<td>8</td>
<td></td>
<td>Std. Mean Difference (IV, Fixed, 95% CI)</td>
<td>Subtotals only</td>
</tr>
<tr>
<td>- DQ (BSID- MDI, Griffiths GCI)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1.1 Parent-infant relationship</td>
<td>1</td>
<td>42</td>
<td>Std. Mean Difference (IV, Fixed, 95% CI)</td>
<td>0.73 [0.11, 1.36]</td>
</tr>
<tr>
<td>1.2 Infant development</td>
<td>3</td>
<td>334</td>
<td>Std. Mean Difference (IV, Fixed, 95% CI)</td>
<td>0.39 [0.17, 0.61]</td>
</tr>
<tr>
<td>1.3 Parent-infant relationship and Infant development</td>
<td>4</td>
<td>978</td>
<td>Std. Mean Difference (IV, Fixed, 95% CI)</td>
<td>0.51 [0.38, 0.64]</td>
</tr>
<tr>
<td>2 Cognitive outcome at pre-school age - IQ (Stanford Binet, McCarthy)</td>
<td>2</td>
<td></td>
<td>Std. Mean Difference (IV, Fixed, 95% CI)</td>
<td>Subtotals only</td>
</tr>
<tr>
<td>2.1 Parent-infant relationship</td>
<td>0</td>
<td>0</td>
<td>Std. Mean Difference (IV, Fixed, 95% CI)</td>
<td>Not estimable</td>
</tr>
<tr>
<td>2.2 Infant development</td>
<td>0</td>
<td>0</td>
<td>Std. Mean Difference (IV, Fixed, 95% CI)</td>
<td>Not estimable</td>
</tr>
<tr>
<td>2.3 Parent-infant relationship and Infant development</td>
<td>2</td>
<td>961</td>
<td>Std. Mean Difference (IV, Fixed, 95% CI)</td>
<td>0.48 [0.35, 0.61]</td>
</tr>
<tr>
<td>3 Cognitive outcome at school age</td>
<td>3</td>
<td></td>
<td>Std. Mean Difference (IV, Fixed, 95% CI)</td>
<td>Subtotals only</td>
</tr>
<tr>
<td>- IQ (WISC, Kaufmann)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3.1 Parent-infant relationship</td>
<td>0</td>
<td>0</td>
<td>Std. Mean Difference (IV, Fixed, 95% CI)</td>
<td>Not estimable</td>
</tr>
<tr>
<td>3.2 Infant development</td>
<td>1</td>
<td>126</td>
<td>Std. Mean Difference (IV, Fixed, 95% CI)</td>
<td>-0.12 [-0.47, 0.23]</td>
</tr>
<tr>
<td>3.3 Parent-infant relationship and Infant development</td>
<td>2</td>
<td>925</td>
<td>Std. Mean Difference (IV, Fixed, 95% CI)</td>
<td>0.04 [-0.09, 0.18]</td>
</tr>
<tr>
<td>4 Motor outcome at infant age (BSID PDI, Griffiths locomotor)</td>
<td>6</td>
<td></td>
<td>Std. Mean Difference (IV, Fixed, 95% CI)</td>
<td>Subtotals only</td>
</tr>
<tr>
<td>4.1 Parent-infant relationship</td>
<td>0</td>
<td>0</td>
<td>Std. Mean Difference (IV, Fixed, 95% CI)</td>
<td>Not estimable</td>
</tr>
<tr>
<td>4.2 Infant development</td>
<td>2</td>
<td>157</td>
<td>Std. Mean Difference (IV, Fixed, 95% CI)</td>
<td>0.26 [-0.05, 0.58]</td>
</tr>
<tr>
<td>4.3 Parent infant relationship/ infant development</td>
<td>4</td>
<td>992</td>
<td>Std. Mean Difference (IV, Fixed, 95% CI)</td>
<td>0.02 [-0.11, 0.15]</td>
</tr>
<tr>
<td>5 Motor outcome at school age (Griffiths locomotor)</td>
<td>1</td>
<td></td>
<td>Std. Mean Difference (IV, Fixed, 95% CI)</td>
<td>Subtotals only</td>
</tr>
<tr>
<td>5.1 Parent-infant relationship</td>
<td>0</td>
<td>0</td>
<td>Std. Mean Difference (IV, Fixed, 95% CI)</td>
<td>Not estimable</td>
</tr>
<tr>
<td>5.2 Infant development</td>
<td>1</td>
<td>49</td>
<td>Std. Mean Difference (IV, Fixed, 95% CI)</td>
<td>-0.34 [-0.91, 0.23]</td>
</tr>
<tr>
<td>5.3 Parent infant relationship/ infant development</td>
<td>0</td>
<td>0</td>
<td>Std. Mean Difference (IV, Fixed, 95% CI)</td>
<td>Not estimable</td>
</tr>
<tr>
<td>6 Rate of cerebral palsy</td>
<td>4</td>
<td></td>
<td>Risk Ratio (M-H, Fixed, 95% CI)</td>
<td>Subtotals only</td>
</tr>
<tr>
<td>6.1 Parent-infant relationship</td>
<td>0</td>
<td>0</td>
<td>Risk Ratio (M-H, Fixed, 95% CI)</td>
<td>Not estimable</td>
</tr>
<tr>
<td>6.2 Parent-infant relationship and infant development</td>
<td>1</td>
<td>317</td>
<td>Risk Ratio (M-H, Fixed, 95% CI)</td>
<td>0.78 [0.39, 1.59]</td>
</tr>
<tr>
<td>6.3 Infant development</td>
<td>3</td>
<td>269</td>
<td>Risk Ratio (M-H, Fixed, 95% CI)</td>
<td>1.17 [0.56, 2.46]</td>
</tr>
<tr>
<td>6.4 Parent support</td>
<td>0</td>
<td>0</td>
<td>Risk Ratio (M-H, Fixed, 95% CI)</td>
<td>Not estimable</td>
</tr>
</tbody>
</table>