Effect of early intervention in infants at very high risk of cerebral palsy: a systematic review

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ABBREVIATIONS

AACPDM	American Academy for Cerebral Palsy and Developmental Medicine
COPCA	COPing with and CAring for infants with special needs programme
GAME	Goals, Activity and Motor Enrichment programme
MDI	Mental Developmental Index of the Bayley Scales of Infant Development
NDT	Neurodevelopmental treatment
PDI	Psychomotor Developmental Index of the Bayley Scales of Infant Development
RCT	Randomized controlled trial
VHR	Very high risk

AIM First, to systematically review the evidence on the effect of intervention applied during the first postnatal year in infants with or at very high risk of cerebral palsy (CP) on child and family outcome. Second, to assess whether type and dosing of intervention modify the effect of intervention.
METHOD Relevant literature was identified by searching the PubMed, Embase, and CINAHL databases. Selection criteria included infants younger than 12 months corrected age with or at very high risk of CP. Methodological quality including risk of bias was scrutinized.
RESULTS Thirteen papers met the inclusion criteria. Seven studies with moderate to high methodological quality were analysed in detail; they evaluated neurodevelopmental treatment only (n=2), multisensory stimulation (n=1), developmental stimulation (n=2), and multifaceted interventions consisting of a mix of developmental stimulation, support of parent–infant interaction, and neurodevelopmental treatment (n=2). The heterogeneity precluded conclusions. Yet, two suggestions emerged: (1) dosing may be critical for effectiveness; (2) multifaceted intervention may offer best opportunities for child and family.
INTERPRETATION The literature on early intervention in very high-risk infants with sufficient methodological quality is limited, heterogeneous, and provides weak evidence on the effect. More studies are urgently needed. Suggestions for future research are provided.

It is generally agreed that infants biologically at high risk of developmental disorders, such as infants born preterm or infants with neonatal encephalopathy, should receive early intervention.[1] The rationale underlying this idea is threefold. First, the prenatal, perinatal, and neonatal events that occurred in the at-risk infant may have affected the infant's brain. This may have been a direct effect – that is, the event may have resulted in a lesion of the brain, for example periventricular leukomalacia or a cortical infarction[2,3] – or an indirect effect, for instance caused by the pain and stress related to being nursed in the neonatal intensive care unit.[4,5] Second, if the adversities of early life did have a negative impact on the infant's brain, then early life is the period that has the highest potential of being able to counteract the negative sequelae because of the high plasticity of the young brain.[6] Third, families of infants who have been admitted to the neonatal intensive care unit are in need of guidance.[7] Assistance is needed to cope with the immediate and potentially prolonged traumatic effects of the turbulent events associated with the sudden admission of the infant to intensive care. In addition, parents need to learn to understand the behaviour of the infant that may differ from infants with typical development.[8] For instance, the infant may be irritable, may have problems in self-regulation, may be floppy or stiff, or show signs of transient dystonia.[7,9,10] This implies that support of parent–infant interaction may be one of the primary needs of families of high-risk infants.

The effect of early intervention in infants biologically at risk of developmental disorders has been particularly studied in infants born preterm. The recent Cochrane review of Spittle et al.[1] concluded that early intervention in infants born preterm is associated with an improved

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cognitive development during infancy and preschool age and a minor positive effect on infant motor development. Interestingly, the generally positive effects of early intervention occur in the presence of a large variety in theoretical concepts and actual content of the intervention programmes. Nevertheless, within the heterogeneity in programme content, most early intervention programmes for infants born preterm include a family component.[11] Evidence is emerging that interventions that focus on parent–infant relationships have a greater impact on cognitive outcomes at infancy and preschool age than intervention programmes that focus on either infant development or parent support.[1] Infants born preterm only form a part of the infants in need of early intervention. Two other groups also require developmental support. Worldwide, the largest group consists of infants born in socially disadvantaged conditions. These infants are socially and biologically at risk of developmental disorders.[12] Whether or not early intervention by home programmes may be effective in promoting developmental outcome of these infants is currently not clear.[13,14] The other group consists of infants born at term who suffered from perinatal adversities and/or presented with signs of neurological dysfunction or developmental delay. The effect of early intervention in these infants has been studied less. The available data point to a similarly large variation in intervention approaches as present in early intervention in infants born preterm.[15] The systematic review of Blauw-Hospers et al.,[15] which included both infants born at term and at-risk infants born preterm, concluded that programmes aiming at developmental stimulation are associated with improved motor and cognitive development. Yet no evidence was available that early intervention on the basis of neurodevelopmental treatment (NDT) or treatment according to Vojta is associated with a better developmental outcome.[15,16]

Infants with a significant lesion of the brain, such as periventricular leukomalacia, peri/intraventricular haemorrhage with a severity of at least grade II, or perinatal stroke, certainly deserve early intervention as they are at very high risk of developmental disorders. For instance, the chance to be diagnosed with cerebral palsy (CP) varies from about 85% in infants with cystic periventricular leukomalacia to about 30% in infants with term stroke.[17] Yet little is known about the effect of early intervention in infants with a significant lesion of the brain. The lack of knowledge on early intervention in these infants may be attributed to the relatively low prevalence of significant brain injury at early age. Assuming that the rate of significant early brain injury is about twice the prevalence rate of CP, it may be estimated that in Western industrialized countries the prevalence of a significant lesion of the brain at early age is 10% to 20% in infants born preterm and 2‰ to 3‰ in infants born at term.[18,19]

For many years it has been rather difficult to detect infants with a significant lesion of the brain at early age. However, owing to increasing technology and insight into the developing brain, this perspective has changed.

What this paper adds

- Evidence of effect of early intervention during the first postnatal year in infants at very high risk of cerebral palsy is weak.
- Suggests dosing may be critical in the effectiveness of early intervention.
- Suggests multifaceted intervention may be more effective than single component intervention.

Currently, neonatal magnetic resonance imaging and diagnostics by the assessment of general movements are powerful tools for detecting – within the group of infants referred to neonatal care – an early lesion of the brain and a very high risk of CP.[20,21] This means that times are changing and that interest in studying the effect of early intervention in infants with or at very high risk of CP (VHR infants) is increasing rapidly. This is reflected by the two recent reviews of Morgan et al.[22,23] These systematically assessed the effect of early intervention provided between birth and 2 years of age; they focused on early motor intervention and motor outcomes. The first review by Morgan et al.[22] addressed the effect of environmental enrichment in VHR infants and children (0–96mo corrected age). It concluded that provision of an enriched environment is associated with a small positive effect on motor outcome. The second review[23] had a wider approach. It assessed the effect of any type of early motor intervention on any type of outcome, in which it focused on the effect sizes on motor outcome. It concluded that the two interventions that had shown a moderate to large effect on motor outcome shared the incorporation of child-initiated movement, modification, or enrichment of the environment, and task-specific training. The two interventions were evaluated in the influential study of Palmer et al.,[24] which evaluated the effect of intervention applied in children with CP during their second year of life, and in the pilot study of Morgan et al.,[25] which evaluated intervention in 13 very high-risk infants.

The aim of the present study is to systematically and critically review the literature on the effect of early intervention in the first year after birth in infants with CP or at very high risk of CP. Our study has two specific foci. First, we focus on the first year after birth because it is the period of postnatal life with the highest rate of developmental changes in the brain.[6] Second, we pay detailed attention to methodological quality, as the analysis of strengths and weaknesses of existing studies may pave the way for future studies with a strong design. To this end we first evaluate the studies' overall methodological quality. Next, studies with a moderate to strong methodological quality are scrutinized for strong and weak methodological characteristics. Finally, we assess the effect of early intervention in the studies with moderate to strong methodological quality by addressing the following two questions: (1) is early intervention in VHR infants associated with improved motor and cognitive development; and (2) is early intervention in VHR infants associated with improved family or parental outcome? Special attention is paid to the question of whether the effect of intervention is affected by (1) the nature of the risk of the infants, for example the type of lesion

of the brain, and (2) the contents of the intervention, namely the type and dosing of the intervention.

We hypothesized that: (1) early intervention is associated with improved cognitive and motor outcomes and (2) that the effect is dosage dependent; (3) early intervention is associated with improved family outcomes, especially when intervention programmes pay specific attention to parental or family well-being; (4) early intervention is less effective in improving child outcome in infants with periventricular leukomalacia than in infants with other brain lesions, as periventricular leukomalacia is associated with the highest risk of CP.[17] This means that our review is complementary to the recent review of Morgan et al.[23] It differs by its two points of specific attention – focusing on intervention during the first year after birth and on methodological quality – and by not focusing on effect sizes in motor outcome but by paying equal attention to the child's motor and cognitive outcome and parameters of family well-being. In addition, it addresses the questions of effect modification by the nature of the risk and the dosing and type of intervention. We conclude our paper with suggestions for early intervention in VHR infants, including a list of ideas for future research.

METHOD

Search strategy and evaluation procedure

A literature search was performed to identify studies published from 1952 to January 2016. Electronic databases searched were PubMed, Embase, and CINAHL. Details of the search, including inclusion and exclusion criteria, are provided in Appendix S1 (online supporting information).

For the evaluation of methodological quality a three-step procedure was used (see Appendix S2, online supporting information; in line with the PRISMA-P statement[26]). First, the level of evidence according to Sackett et al.[27] and an evaluation of the methodology criteria of the Academy for Cerebral Palsy and Developmental Medicine (AACPDM) for group design studies (revision 1.2, 2008 version)[28] was performed. This resulted in a classification of strong, moderate, or weak methodological quality. The next two steps were only performed in studies with moderate to strong quality. The steps consisted of the application of the criteria of Mallen et al.[29] (maximum score indicating highest quality: 25 points) and the Cochrane Risk of Bias assessment.[30]

RESULTS

Study selection and methodological quality

Figure S1 (online supporting information) shows the selection of the articles. The database searches yielded 1125 articles, of which 1089 were excluded on the basis of screening of title and abstract. We assessed the full text of the remaining 36 papers. Twenty-three were excluded, as they did not meet the inclusion criteria. The remaining 13 articles – reporting on 11 studies – were reviewed in detail (Table I). For details on study selection see Appendix S2. Application of the AACPDM criteria revealed that seven of the 11 studies had a moderate to strong methodological quality. In the remaining seven studies the detailed analyses of methodological quality on the basis of the Mallen score and the risk of bias evaluation were performed (see Table II and Appendix S2). The analyses demonstrated considerable heterogeneity in methodological quality.

Contents of the studies

Study characteristics and outcome measures

The characteristics and outcomes of the seven studies are summarized in Table SII (online supporting information). The seven studies evaluated the effect of intervention in 299 infants (study groups n=149; comparison groups n=150), all by means of small RCTs. The group sizes varied from 6 to 51 in the study groups (median n=17), and from 7 to 54 in the comparison groups (median n=12). Weindling et al.[31] contributed most infants, namely 35% of all infants studied.

Five studies included infants on the basis of a lesion of the brain,[31–33] a lesion of the brain or clear neonatal neurological deviancy,[34] or high suspicion of CP.[35] The lesions of the brain consisted of periventricular leukomalacia (grades II–III according to De Vries et al.,[36] but not always specified[32]) or intraventricular haemorrhage, Papile[37] grades II to IV[33] or III to IV[31,32] diagnosed by neonatal cranial ultrasound. The other two studies[25,38,39] included infants on the basis of definitely abnormal general movements between 10 weeks and 18 weeks corrected age, indicating a very high risk of CP.[40,41]

The child's developmental outcome was assessed with a large variation of instruments and at varying points in time. Five studies started with an assessment of the infant's developmental status before the onset of intervention, but two did not.[31,32] Three studies evaluated development during the intervention,[33,34,38,39] all studies assessed outcome immediately after the end of the randomized intervention, and four studies evaluated whether effects of intervention were retained.[31,32,34,38,39] In the evaluation of developmental outcome the studies focused on motor and cognitive development (n=7 and n=6 studies respectively), generally using standardized tests with well-established psychometric properties.[42] For the evaluation of motor development the Griffith Developmental Scales,[31,43] Alberta Infant Motor Scale,[39,44] Bayley Scales of Infant Development,[32–34,45] Infant Motor Profile,[38,46] and the Peabody Developmental Motor Scales[25,47] were used. Cognitive development was assessed with the Griffith Developmental Scales[31] and the Bayley Scales of Infant Development.[32–34,39,45] Two studies included a neurobehavioural assessment (the Neonatal Behavioural Assessment Scale[48])[33] or a detailed neurological examination (Hempel assessment[49,50]).[39] Finally three studies included activities of daily living by using the Pediatric Evaluation of Disability Inventory,[39,51] the Goal Attainment Scaling,[25,52] and Canadian Occupational Performance Measure[25,53] or a non-standardized questionnaire.[35]

Table I: Studies included in the review, methodology assessment according to the American Academy for Cerebral Palsy and Developmental Medicine (AACPDM)[a]

Study	Research design	Level of evidence[b]	AACPDM conduct questions[c]							Quality scores	Quality summary
			1[d]	2[d]	3	4[d]	5	6[d]	7[d]		
Scherzer et al.[102]	RCT	II	No	No	No	Yes	No	Yes	No	2	Weak
d'Avignon et al.[103]	RCT	II	Yes	No	No	No	No	Yes	No	2	Weak
Mayo[35]	RCT	II	Yes	No	No	Yes	No	Yes	Yes	4	Moderate
Weindling et al.[31]	RCT	II	No	No	Yes	Yes	Yes	Yes	Yes	5	Moderate
Nelson et al.[32]	RCT	II	Yes	Yes	Yes	Yes	No	No	No	4	Moderate
Ohgi et al.[33]	RCT	II	No	No	Yes	Yes	Yes	No	Yes	4	Moderate
Badr et al.[34]	RCT	II	Yes	Yes	Yes	Yes	No	No	Yes	5	Moderate
Campbell et al.[72,104]	RCT	II	No	No	Yes	Yes	No	Yes	No	3	Weak
Lowes et al.[105]	Pretest–post-test cohort	IV	Yes	Yes	Yes	No	No	No	No	3	Weak
Hielkema et al.[38]; Blauw-Hospers et al.[39]	RCT	II	Yes	No	Yes	Yes	Yes	Yes	Yes	6	Strong
Morgan et al.[25]	RCT	II	Yes	Yes	Yes	Yes	No	Yes	No	5	Moderate

[a]Criteria for methodological quality assessment according to the AACPDM (revision 1.2)[28] with adjustments for the current study in italics. [b]Level of evidence from Sackett et al.[27] [c]1: Were inclusion and exclusion criteria of the study population well described and followed? *Both inclusion and exclusion criteria need to be met to score 'yes'.* 2: *Were* the intervention *and comparison condition* well described and was there adherence to the intervention assignment? Both parts of the question need to be met to score 'yes'. *Adherence to intervention implies that adherence is assessed in a systematic way (questionnaire, video) and that >65% of planned intervention was achieved. The cut off of 65% adherence was an arbitrary one based on common sense; it meant that about two-thirds of the intervention had been achieved.* 3: Were the measures used clearly described, valid and reliable for measuring the outcomes of interest? 4: Was the outcome assessor unaware of the intervention status of the participants (i.e. *was it explicitly described* that the assessors were masked)? 5: Did the authors conduct and report appropriate statistical evaluation: that is, did they perform proper statistics and did they include a power calculation (the latter did not need to result in the demonstration of group sizes allowing for adequate power)? Both parts of the question need to be met to score 'yes'. 6: Were dropout/loss to follow-up *after start of the intervention* reported and <20%? For two-group designs, was dropout balanced? *Note that dropouts due to death are excluded from the dropout calculation.* 7: Considering the potential within the study design, were appropriate methods for controlling confounding variables and limiting potential biases used? *Studies with groups with n<10 at the end of the intervention – either because they started with small groups or attrition resulted in groups with fewer than 10 participants – are assigned 'no', as the small number precludes multivariable statistics to control for confounders.* Methodological quality is judged – according to the AACPDM criteria – as strong ('yes' score on ≥six questions), moderate (score 4 or 5), or weak (score ≤3). [d]Criteria that address the risk of bias within studies. RCT, randomized controlled trial.

Table II: Cochrane risk of bias assessment

Risk of bias criteria	Mayo[35]	Weindling et al.[31]	Nelson et al.[32]	Ohgi et al.[33]	Badr et al.[34]	Hielkema et al.[38,39]	Morgan et al.[25]
Selection bias							
Random sequence generation	Low[a]	Unclear	Low[a]	Low	Low[a]	Low[a]	Low
Allocation concealment	Low[a]	Low	Low[a]	Unclear	Low[a]	Low[a]	Low
Performance bias							
Blinding of participants and personnel	High	High	High	High	High	High	High
Detection bias							
Blinding of outcome assessment	High[a]	Low	Low	Low	Low	Low	Low
Attrition bias							
Incomplete outcome data	Low	Low	High	High	High	Low	Low
Reporting bias							
Selective reporting	High	Low	Low	Low	Low	Low	Low
Other bias							
Other sources of bias[b]	High	High	High	High	High	High	High

[a]Determined on the basis of additional information provided by the authors. [b]See Table SI (online supporting information).

Five studies included parental or family outcomes. Three studies addressed mental health of the primary caregiver[25,33,34] and two studies[32,34] evaluated mother–infant interaction. The instruments are discussed in the next section in association with the results they generated.

Type, frequency, duration, and effect of early intervention

The heterogeneity in study design, especially in the intervention programmes applied, precluded an integrated presentation or meta-analysis of the findings. Therefore the seven studies are summarized separately (Table SII).

Montreal study. Mayo[35] randomized 4- to 18-month-old VHR infants in 1983 to 1984 for receiving either intensive (1/wk; *n*=17) or standard physiotherapy (1/mo; *n*=12) for 6 months. In both, physiotherapy was based on NDT, including parental instructions on positioning, handling, and stimulation of the infant. Outcome measures assessed primitive reflexes, postural reactions, gross and fine motor

skills, abnormal movements, activities of daily living, and the Mental Developmental Index (MDI) items of the Bayley Scales of Infant Development, yielding an aggregate score.

At the end of the intervention, 12 infants in the intensive therapy group (71%) and eight infants in the other group (67%) were diagnosed with CP. The former group improved significantly more than the latter, with all measurements contributing to the effect. The strength of the study was its relatively simple design, the only difference in intervention between groups being the intensity. The major limitations were the broad range in age at study entry, evaluation with non-standardized, non-validated tests, and the use of an aggregate score with the risk of reporting bias.

Liverpool study. Weindling et al.[31] included infants from a single hospital over a 43-month period on the basis of ultrasonographic signs of periventricular leukomalacia grades II to III[36] or intraventricular haemorrhage grades III to IV on neonatal scans.[37] Infants were randomized into an intervention (n=51) and a comparison group (n=54). The intervention consisted of weekly NDT-based physiotherapy guidance at home from term age to 12 months corrected age, focusing on parental handling and developmental stimulation in daily life. Intervention frequency decreased to once every 2 weeks between 6 months and 9 months, and once a month between 9 months and 12 months if the paediatrician noted favourable development of the infant. Comparison infants received standard care, but when the paediatrician noticed during follow-up that the infant developed CP, the child received physiotherapy guidance once a week.

Outcome (Griffith Developmental Scales) at 12 months corrected age, i.e. when intervention was complete, and at 30 months corrected age (study group n=42; comparison group n=41) showed no difference between the groups or between subgroups with and without CP (about 50% in each group were diagnosed with CP). The study was adequately powered. The major limitation was the lack of information on the actual content of and adherence to intervention, including the fact that over time the intervention in both groups increasingly overlapped.

Chicago study. Nelson et al.[32] recruited in 1993 to 1997 a group of 21 neonates with periventricular leukomalacia (grades not specified) or intraventricular haemorrhage grades III to IV on ultrasonography. Randomization allocated 10 infants with a brain lesion in the study group and 11 in the comparison group (standard care). Randomized intervention, provided from 33 weeks gestational age to 2 months corrected age, consisted of auditory (human voice), tactile (stroking), visual (eye-to-eye), and vestibular (rocking) stimulation twice a day for 15 minutes for 5 days a week at the hospital (by a research assistant), then at home (by a parent). Self-reported maternal compliance when the infant was 2 months corrected age was reported as 87%.

Outcome assessment focussing on mother–infant interaction at 2 months and 4 months corrected age suggested that comparison mothers and infants scored better than the study dyads, but the data suffered from substantial risk of bias, including attrition (2mo, 35%; 4mo, 49%). At 12 months corrected age the proportion of children 'diagnosed with CP' was similar in both groups and there were no significant differences in motor or cognitive outcomes. The strength of the study was its evaluation of both infant and parent outcomes. The major limitations consisted of the small study groups, the partly combined analysis with a group of infants with no brain lesions, and the high risk of attrition bias.

Nagasaki study. Ohgi et al.[33] recruited from 1997 to 2002 in one hospital 23 infants with periventricular leukomalacia grades II to III or intraventricular haemorrhage grades III to IV on neonatal ultrasonograpy. Randomized intervention (n=12 vs n=11 receiving standard care) had two parts. Before term age, mothers received instruction on intervention based on the Neonatal Behavioural Assessment Scale, aiming to facilitate development by enhancing parenting skills. The second part consisted of parental education on how to promote their infant's development, including adapting the sensory environment and normalizing the infant's posture and muscle tone with NDT-based techniques. The intervention sessions lasted 40 to 60 minutes, and took place once a week or every other week between term age and 6 months corrected age.

Outcome was assessed at term age and 1 month corrected age with the Neonatal Behavioural Assessment Scale, and immediately after completion of the intervention at 6 months corrected age with the Bayley Scales of Infant Development. In addition, maternal anxiety status[54] and maternal self-efficacy[55] were assessed. At 1 month corrected age there were no significant group differences. However, study infants showed a significant improvement between term age and 1 month on the domains orientation and state regulation, whereas comparison infants lacked a similar improvement. The Bayley scores showed no significant group differences at 6 months corrected age. Maternal anxiety significantly decreased and self-efficacy significantly increased in the study group but not in the comparison group. A major strength of the study was its evaluation of both child and parental outcomes. Major limitations included small group sizes, short follow-up (precluding information on the proportion of children with CP), and some attrition bias.

Southern California study. Badr et al.[34] recruited 62 VHR infants on the basis of neonatal neuroimaging or neonatal neurological status. Infants with intraventricular haemorrhage grade IV with periventricular leukomalacia or severe cortical destruction or atrophy were excluded. Randomization allocated 32 infants in the intervention group and 30 in the comparison group (standard care). Randomized intervention – provided from birth to 12 months corrected age – consisted of the Curriculum and Monitoring System[56] method comprising cognitive, motor, and language activities for developmental stimulation. Intervention was provided at home with a frequency that decreased with

increasing infant age. Families were instructed to perform intervention activities for 20 minutes a day.

Outcome was assessed up and until 18 months corrected age (attrition 31%). No information on the diagnosis of CP was provided. Motor outcome measured with the PDI was similar in both groups, but cognitive development differed: the MDI scores of the comparison infants gradually decreased with increasing age. At 6 months corrected age, mother–infant interaction[57]) in the intervention group was significantly better than in the comparison group. At older infant ages, this difference disappeared. Outcome on other measures of mother–infant interaction[57] and parental well-being[58] did not differ. The strengths of the study were its relatively large group sizes and the broad range of outcome measures, including family outcomes. Its major limitations were the parsimonious documentation of brain lesions and neurological outcome, and attrition bias.

Groningen study. The Groningen VIP study[38,39] recruited in 2003 to 2005 in one hospital 46 infants who presented with definitely abnormal general movements at 10 weeks corrected age. Six infants (13%) had a significant lesion on neonatal ultrasonography (periventricular leukomalacia grades II–III or IVH grades III–IV). Randomization allocated 21 infants in the study group and 25 in the comparison group. The randomized intervention was provided at home between 3 months and 6 months corrected age, and consisted of the COPCA programme (COPing with and CAring for infants with special needs – a family-centred programme[59,60]). The COPCA programme has two components: a family and a neurodevelopmental component. The family component uses family coaching to support family autonomy and participation. Key notions of the neurodevelopmental component are 'hands-off', self-initiated activity, variation, challenge, and trial-and-error learning. COPCA was delivered at home twice a week. The comparison intervention (typical infant physiotherapy; 1/wk) consisted of standard physical therapy implying a mix of a functional approach[61] and NDT.

Outcome was assessed up and until 18 months corrected age with a battery of tests. The contents of study and comparison interventions were assessed by videotaping intervention sessions, resulting in quantitative parameters of intervention contents. Family adherence was assessed in an indirect way, by means of a quantitative analysis of caregiving behaviour during infant bathing.[62]

Outcome in the two randomized groups was virtually similar. At 18 months corrected age five children in each group were diagnosed with CP. However, a small cognitive advantage for the COPCA group was found that was restricted to families with a mother with relatively little education. The quantitative analysis of the intervention sessions demonstrated clear differences between the COPCA and typical infant physiotherapy programmes, but also substantial overlap in contents.[59] The analysis of associations between specific physiotherapeutic actions during intervention and developmental outcomes revealed that the associations differed for children who were diagnosed with CP and children without CP. In children diagnosed with CP, coaching of caregivers and offering the infant challenging motor activities were associated with better outcomes at 18 months corrected age. In the children without CP, sensory and passive experiences were associated with higher MDI scores at 6 months, whereas NDT hands-on techniques were associated with worse functional mobility at 18 months corrected age. The video analysis of the bathing sessions revealed that the type of intervention affected the position in which parents bathed their infants immediately post-intervention: COPCA intervention was associated with the infant being held more in the challenging sitting position than typical infant physiotherapy. Being bathed in sitting position at 6 months was associated with better functional mobility at 18 months corrected age.[62] These data suggest that early intervention may affect parental behaviour during daily care giving activities, and that this behaviour may be associated with an effect on child development.

Recently over 90% of the participants were reassessed at school age (7y 6mo–10y; E G Hamer et al., personal communication 2016). Developmental outcome of study children did not differ from that of the comparison group. Also, parental mental health was similar in both groups. However, the families differed in one aspect of educational approach: COPCA parents used the 'try it yourself approach' more often than comparison parents, meaning that when the child tried to master a new skill, they were allowed to try out by trial and error until success was achieved. This educational approach showed a positive correlation with the proportion of early intervention time spent with family coaching and the infant being allowed to produce self-initiated movements, and a negative correlation with the proportion of time spent with NDT facilitation techniques. In addition, process analyses showed that more intervention time spent with training and strict instructions of the parents was associated with lower mobility scores (measured with the Developmental Coordination Questionnaire).[63]

The study had a strong methodological quality due to the long-term follow-up with little attrition, adequate power, and detailed documentation of the intervention, allowing process evaluation. The ecological approach was a strength and a limitation, as adherence could only be assessed indirectly. The limitations of the study were the heterogeneity in physiotherapy with content-overlap in study and comparison groups, the relatively low proportion of children with CP, and the lack of information on family outcome up to 18 months corrected age.

Australian study. The pilot study of Morgan et al.[25] recruited, in 2011 to 2012, 13 infants from six Australian neonatal intensive care units who showed definitely abnormal general movements without fidgety movements at 3 to 5 months corrected age indicating a very high risk of CP.[20,21,40,41,64,65] No data on brain imaging were reported. Randomized intervention (n=6 vs n=7 receiving standard care) started between 3 months and 5 months corrected age and was provided for 3 months. The experimental

intervention consisted of the GAME (Goals, Activity and Motor Enrichment) programme. The GAME programme has three components. (1) Goal-oriented activity-based motor training with parental identification of goal areas for practice. Therapists scaffold the motor tasks so that the infant is always able to accomplish part of the task. Infant practice may involve manual assistance of the therapist or parent ('hands-on'). The motor activity training is summarized in a written home programme. (2) Parent education on the infant's motor capacities and methods to stimulate developmental progress. (3) Environmental enrichment, meaning that parents are encouraged and assisted to set up motor-enriched play environments to promote child self-initiated movements, exploration, and task success. GAME was delivered at home once a week with sessions of 60 to 90 minutes. The comparison group received standard physiotherapy intervention consisting of a mix of guidance on the basis of motor learning principles and NDT. Adherence to intervention was assessed with parental logbooks (total session time in study group: 10h; comparison group: 3.5h; time spent performing therapist recommendations at home: total practice time in study group [*n*=6] 141h; comparison group [*n*=5] 54h).

Outcome was assessed at baseline and immediately after the intervention. The infant outcomes focused on motor outcome, in particular motor activities in daily life, by using the Goal Attainment Scaling, Canadian Occupational Performance Measure, and Peabody Developmental Motor Scales. Family outcome was evaluated with the Home Observation Measure of the Environment,[66] and the Depression, Anxiety and Stress Scale (DASS)-21, a self-report measure assessing depression, anxiety, and stress.[67] Developmental outcome of both groups on the Goal Attainment Scaling and Canadian Occupational Performance Measure was similar. Yet, motor outcome assessed with the Peabody Scales was significantly better in the GAME group than in the comparison group. It should be noted, however, that at 5 to 12 months corrected age four of the six study infants were diagnosed with CP and six of the seven comparison infants. This difference may have contributed to or confounded the difference in motor outcome between the groups. The Home Observation Measure of the Environment scores improved comparably in both groups. Also, the parental DASS-21 scores in both groups did not differ significantly.

The pilot nature of the study, with limited group sizes, resulted in a moderate methodological quality. A major strength of the study was its detailed description of the experimental intervention and the good documentation of the adherence to intervention. The limited information on the comparison intervention and participant recruitment, the lack of information on brain lesions, and the young age at diagnosis of CP were limitations of the study.

DISCUSSION

This systematic review has aimed to critically evaluate the effect of early intervention in the first year after birth on child and family outcomes in infants at very high risk of CP. Over a period of about 30 years (1983–2012), seven studies with moderate to strong methodological quality have been performed. The studies consisted of small RCTs that evaluated the effect of early intervention in 299 infants.

Methodological considerations

Only one study[38,39] had a strong methodological quality; the others had a moderate methodological quality, often related to small sample sizes providing weak evidence at best (see Table III). In most studies, selection bias was prevented, though this was often not reported. Future studies should include information on random sequence generation and concealment of group allocation in study design and report. All studies had a high risk of performance bias as families and professionals providing the intervention were aware of the type of intervention. However, this risk is typically unavoidable in early intervention studies. Five other methodological problems and sources of bias occurred relatively often.

First, the disease state was not always well defined. Most studies included infants on the basis of a brain lesion determined with neonatal ultrasonography. Often, however, timing of the ultrasound scan(s) or lesion classification system were not reported, though this influences predictive validity of the reported abnormalities.[36] Neuroimaging may consist of sequential cranial ultrasound or magnetic resonance imaging.[68]

Second, follow-up was generally short, which may have interfered with a reliable assessment of the diagnosis CP. Only two studies assessed all children with a standardized neurological examination at a minimum age of 18 months.[31,38,39] It is debatable at which age a diagnosis of CP can be reliably determined. A recent Danish study indicated that in half of the children with CP the diagnosis can be established before 12 months corrected age.[69] Yet others stress that the expression of neurological signs during infancy, also in children later diagnosed with CP, is often characterized by instability and change.[70] In line with this observation, national CP registries recommend that the final age of ascertainment of the diagnosis CP is at least 4 years.[71]

Third, the description of the comparison intervention was often minimal. It consisted in four studies[31–34] of the notion of 'standard care' without further description. Most likely it meant that the families did not receive a specific form of early intervention. In two studies[25,38,39] the comparison intervention consisted of standard paediatric physiotherapy. However, it is hard to know what that means, as it is well known that standard infant physiotherapy is characterized by heterogeneity.[59] Only one study described the comparison intervention in detail on the basis of video evaluation of the actual intervention.[38,39]

Fourth, the evaluation of the adherence to the intervention turned out to be problematic: three studies[31,33,35] did not address adherence; and one study provided marginal

Table III: Overview of findings

Study	Severity		Intervention				Dosing[b]		FU age (mo)	Outcome				Risk of bias[c]
	PVL (%)	CP (%)	'NDT'	Type[a] Sens.	Dev. stim.	Par–child	Professionals	Home		Motor	Cognition	Family		
Mayo[35]		69	+				6mo, 1×/wk, 1h	?	Post[d]		S>C			Rep.
Weindling et al.[31]		52	+				12mo, 1×/wk	?	12 and 30	**S=C**	**S=C**			Other
Nelson et al.[32]		56		+			2mo, 5d/wk, 30min	2mo, 5d/wk, 30min	12	'S>C'	'S>C'			Attr.
Ohgi et al.[33]	83		+	+	+	+	1×/1–2wks, 30–60min	?	6	'S>C'	'S>C'	S↑, C≈		Attr.
Badr et al.[34]	0?	26?			+	+	12mo, 1×/1–2wks	12mo, 20min/d	6, 12, and 18	S=C	S≈, C↓	6mo: S>C		Attr.
Hielkema et al.[38]; Blauw-Hospers et al.[39]		23			+		3mo, 2×/wk, 60min	Ecological	4, 5, 6, and 18	**S=C**	**Subgr S≈, C↓**			Other
Morgan et al.[25]		77?	+		+	+	3mo, 1×/wk, 60–90min	3mo, S:100min/d[e] C:39min/d	Post[d]	S>C		S↑, C≈		Other

Note that five of the seven studies were small feasibility studies, were underpowered, or had a non-validated outcome measure (Mayo); outcomes of the studies with adequate power are indicated in bold type. [a]Type of intervention: 'NDT', physiotherapeutic actions characteristic of neurodevelopmental treatment, such as hands-on techniques; Sens., intervention focusing on sensory stimulation and/or paying specific attention to the infant's sensory thresholds; Dev. stim., intervention focusing on developmental stimulation; Par–child, intervention paying special attention to parent–child interaction. [b]Dosing of intervention: Professionals, provided by professionals; Home, provided by family at home. [c]Main risk of bias, see Table II. Rep., reporting bias; Attr., attrition bias. [d]Post-intervention at varying ages. [e]Calculated on the basis of the authors' report of total number of hours: e.g. 141h in 12wks implies on average 100min/d. FU age, age at follow-up; PVL, periventricular leukomalacia; CP, cerebral palsy; S>C, study group statistically significantly better than comparison infants; 'S>C', trend that study group was better than comparison infants, but no statistically significant difference; ↑, improvement with increasing age; ↓, lower scores with increasing age; ≈, scores stable over time; subgr, subgroup; 6mo, at age 6 months.

information.[32] The Groningen VIP study[38,39] evaluated a family-centred programme with an ecological approach precluding the measurement of 'therapy time'. The study applied an indirect approach by videotaping and quantifying a daily life activity. The results indirectly shed light on parental compliance – i.e. the implementation of the concepts of the intervention programme in daily life.[62] The Australian study[25] assessed adherence with parental logbooks and obtained information on the number of intervention sessions and the hours of daily practice at home (information for 85% of participants). The success in obtaining adherence data in this study was substantially larger than that in the pilot study of Campbell et al.[72] in which a programme with environmental enrichment and developmental stimulation was also evaluated. It is possible that this difference is related to the duration of the intervention, which was longer in Campbell et al. (10mo) than in the Australian study (3mo). The authors of the former study not only reported that families in general practised less than scheduled, but they also indicated that adherence to the programme grew less during the final months of the intervention. It is conceivable that the motivation of families with an infant with special needs has certain limitations. One limitation is the amount of time per day that can be dedicated to the provision of an intervention programme. This issue is addressed in the next paragraph. Another limitation is the motivation to record over prolonged time in detailed logbooks the adherence to intervention. We therefore suggest that future studies adopt user-friendly means to record adherence, for instance by using a dedicated smartphone app, or by videotaping before, during, and after the intervention the specific activities of daily life.

Fifth, only three studies[31,34,38,39] paid attention to the possibility that the effects of intervention were sustained after the period of randomized intervention. In the Liverpool study[31] the similarity in outcome between study and comparison infants after intervention was retained at the age of 30 months. The other two studies[34,38,39] indicated that the difference between the two intervention groups grew with increasing age. In addition, the Groningen VIP study[38,39] also reported that the associations between specific programme contents and outcome were more clear at 18 months than immediately after intervention at 6 months corrected age, especially in the children diagnosed with CP. Long-term follow-up is, however, not easy to achieve, as Badr et al.[34] indicated. Follow-up without attrition is not realistic but carries a high risk of bias. Therefore we suggest that future studies accurately report the attrition for each outcome parameter and the reasons for it.

It is good to realize that the studies generally treated many methodological issues in an appropriate way. For instance, study and comparison infants were recruited in the same period from the same population; studies adjusted for confounding as far as possible (which was often limited owing to small group sizes); inclusion and exclusion criteria, participant characteristics, experimental and comparison interventions, measures, and outcomes were clearly

described; and outcome assessors were masked and funding sources disclosed.

Effects of early intervention

The heterogeneity in applied interventions, especially in type, frequency, and duration of intervention, and – in particular – the mostly limited group sizes precludes firm conclusions. Nevertheless, some trends may be observed (see Table III).

Only three studies[25,33,34] addressed family outcomes. This is surprising because the importance of a family-centred approach in intervention of children at risk of and with CP has been recognized for four decades.[60,73,74] Most intervention programmes addressed the family during the intervention – albeit in varying ways – but four studies[31,32,35,38,39] failed to evaluate the effect of the intervention on family well-being. The remaining three studies (two small ones, one with a moderate size) reported a positive effect of intervention on family well-being; two[25,33] of these studies had paid special attention to parent–child interaction during the intervention. The weak evidence for a positive effect of parental support on well-being of families of VHR infants corresponds to the clear evidence of such an effect in general groups of infants born preterm. In these general groups, parental support and education is associated with reduced maternal anxiety and depression and with improved self-efficacy.[7]

Two studies evaluated the effect of NDT only. In the Liverpool study[31] NDT was provided once a week for a period of 12 months and compared with standard care; in the Montreal study[35] a once-a-week NDT approach was compared with an NDT regimen of once a month over a period of 6 months. The methodologically more robust and longer-lasting Liverpool study found no beneficial effect of NDT on child motor outcome, whereas the weaker Montreal study did. This suggests that no convincing evidence is available that NDT promotes motor development in VHR infants, a conclusion that would be in line with the review of Novak et al.[75] on the effect of intervention programmes in children with CP. However, some caution is warranted.[76] First, it should be realized that the content of NDT changes continuously; it is – as its developers noted – a 'living concept' constantly integrating novel information on neurodevelopment and family care.[77] The fact that the two studies did not provide convincing evidence for the effectiveness of NDT as applied in the 1980s and 1990s does not preclude that current NDT has equally less convincing effects. Second, it is possible that the Liverpool and Montreal studies used an ineffective dosing of NDT, as Tsorlakis et al.[78] showed that in 3- to 14-year-old children with CP the dosing of intervention mattered: NDT applied five times a week resulted in significantly more improvement of motor development than NDT applied twice a week.

The effect of intervention focusing on the sensory input of the infant was only evaluated in the Nelson et al.[32] but the material was too limited to draw conclusions.

Developmental stimulation was applied in four studies; in two studies[25,33] it was combined with elements of NDT (hands-on approaches) and guidance of parent–child interaction with[33] or without[25] special attention to the infant's sensitivity for sensory input. Three[33,34,39] of the four studies evaluated cognitive outcome, with the two largest studies[34,39] reporting a slightly more favourable cognitive development in the study group than in the comparison group. Also, here the weak evidence that developmental stimulation in VHR infants may be associated with improved cognitive outcome corresponds to the strong evidence of a similar effect in general groups of infants born preterm.[1] Motor outcome was evaluated in all four studies applying developmental stimulation, but only one[25] reported a significant positive effect of the intervention. This study, the Australian feasibility study,[25] applied developmental stimulation in combination with elements of NDT and guidance of parent–child interaction. The small Nagasaki study[33] that studied a similarly compounded intervention found a trend of a similar positive effect on motor outcome, whereas the two studies that applied only developmental stimulation did not find an effect on motor development when compared with standard care[34] or standard physiotherapy.[38,39] It is conceivable that the combination of the various approaches in the Australian intervention was crucial for its effect. Which of the specific components contributed most is not clear. Animal studies[79] and the review of Morgan et al.[22] suggest that developmental stimulation and environmental enrichment may promote motor development in VHR infants to some extent. The conclusion of Morgan et al.[22] was based on the two studies in which intervention had the largest effect size: that is, the Australian feasibility study with 13 participants also included in the current review and Palmer et al.[24,80] Palmer et al. studied the effect of 6 months of randomized intervention provided to children with CP in their second postnatal year. The results showed that children who had received the *Learningames* programme, a developmental stimulation programme similar to the Curriculum and Monitoring System,[34,56] had a better motor outcome than the children who had received NDT. However, it is conceivable that the difference in developmental outcome may not only be explained by the difference in the type of intervention, but also by a difference in dosing: in most children NDT was applied at a frequency of only once every 2 weeks, whereas parents applied the *Learningames* programme on a daily basis. Recently, namely after the completion of our data search, Morgan et al.[81] published the results of another RCT in which the effect of the GAME programme was compared with that of standard physiotherapy in 30 VHR infants. The study showed that the infants who had received the GAME programme had a better motor outcome at 12 months corrected age than the comparison infants. However, it was also unclear in this study whether this difference could be attributed solely to the difference in the contents of the intervention programmes, or that a difference in dosing was partly

responsible for the developmental difference: the frequency of therapy sessions and the amount of time that families dedicated to the implementation of the intervention programme favoured the GAME group.

The literature on early intervention in general groups of infants born preterm also suggests that the inclusion of support of parent–infant interaction in the intervention may be associated with a minor profit in infant motor development.[1,82] Whether the addition of hands-on techniques of NDT also contributes to a favourable outcome is not certain. From a theoretical point of view, NDT techniques that apply minimal postural support might be most promising.[83] It is conceivable that, during the first postnatal year, NDT's minimal assistive postural support hands-on techniques applied during the child's self-initiated activities may promote motor development in infants who do develop CP, whereas they may be counterproductive in at-risk infants without a significant brain lesion or in VHR infants who do not develop CP – a notion that is supported by the process analysis results of the Groningen study.[39]

Another factor that may have been critical for the motor effect of the intervention in the Australian feasibility study[25] is the high intensity with which the intervention was provided. Parents reported that they had performed activities of the detailed training programme on average for 100 minutes a day for 12 weeks. That dosing may be a crucial element in the effect of early intervention is also supported by the Groningen VIP study.[38,39] In the Groningen COPCA intervention, physiotherapists coached families on how infant development could be promoted during daily life activities, such as carrying, dressing, bathing, feeding, and playing. The families were informed and learned by trial and error which ways of developmental stimulation worked best in their own setting. The finding of the Groningen study, that the strongest associations between contents of intervention and outcome were not found at 6 months corrected age but first at 18 months corrected age, supports the notion that the amount of practice (either in frequency per unit time or in duration over time) may be a key notion in early intervention. This would correspond to the effect of dosing in older children with CP.[84] Here it is also relevant to consider the following. Motor learning of VHR infants is frequently impaired by deficits in the processing of sensory information[85] and by a reduced exploratory drive.[86] The latter interferes with the intensive exploration that drives typical development;[87,88] for instance, novice walkers spontaneously produce about 14 000 steps a day and about 100 falls.[87] This could imply that VHR infants might especially benefit from activities that challenge them with joy and enhance their drive to explore their own possibilities and those of the environment.

The studies provided too little information on the brain lesions to answer the question of whether the type of brain lesion modified the effect of early intervention. The finding that the effect of intervention was not evidently larger in the two studies with the lowest proportion of children with CP[34,38,39] than in the other studies suggests that the proportion of children diagnosed with CP was not a major factor determining the effect of early intervention in the VHR infants studied.

Strengths and limitations of the review

The strength of the review is its systematic analysis of: (1) the studies' methodological quality including an analysis of the risk of bias; (2) the type and dosing of the intervention; (3) the nature of the risk of the infants who received the intervention; and (4) both infant and family outcomes. Owing to the systematic and more detailed analysis and discussion of methodological quality that has resulted in concrete suggestions for future research, our paper is complementary to the review of Morgan et al.[22] In addition, our review differs from that of Morgan et al.[22] by its focus on the first year of life and its attention to motor, cognitive, and family outcomes.

It may be considered a limitation that we restricted our review to groups of infants with a mean corrected age below 12 months. This was, however, a deliberate choice as we were specifically interested in the effect of intervention during this period of life, which is characterized by high neuroplasticity.[6] Another limitation of the study is that the proportion of infants with CP in the studies varied. All studies included VHR infants, but they used varying inclusion criteria. We suggest that studies that aim for a very high proportion of infants developing CP include infants with periventricular leukomalacia diagnosed with neonatal neuroimaging in combination with definitely abnormal general movements.[20,21] Two caveats for this approach are, however, warranted. First, it should be realized that about half of children with CP have a brain lesion other than periventricular leukomalacia.[89] Second, recent studies suggest that the proportion of neonates presenting with the above-mentioned combination of signs in European countries is steadily decreasing.[90,91] Fortunate as this is, it hampers the possibility of studying the effect of early intervention in this specific, very high risk subgroup. The implication may be that studies on early intervention in VHR infants require a multi-centre approach to compose study groups with subgroups having specific lesions of the brain and group sizes allowing for appropriate power.

Conclusions and suggestions for future research

The seven studies of the current review are mostly too small and too heterogeneous, especially in the type and dosing of interventions, to allow pertinent conclusions on evidence of effects. Knowing that the studies in the review provided weak evidence at best, we consider that the review nevertheless may offer the following suggestions.

Early intervention consisting of a combination of developmental stimulation, including trial-and-error learning in a challenging, enriched environment, and support of parent–infant interaction, and – perhaps – a minimal application of 'hands-on' postural support techniques of NDT,

may be the best means to promoting motor and cognitive development of VHR infants and family well-being. It is conceivable – but evidence has yet to be provided – that the use of action–observation training,[92] intelligent baby gym,[93] and – in infants with clear motor asymmetries – baby constraint-induced movement therapy[94,95] may offer additional ingredients of this multifaceted approach. The contribution of NDT's hands-on techniques in this approach is least certain. It is, however, conceivable that a minimal application of NDT's postural support techniques is beneficial for infants with CP, whereas it is unfavourable for high-risk infants not developing CP.[39] We hypothesize that for early intervention in VHR infants the following strategy may work best: include NDT's minimal assistive postural support hands-on techniques applied during the child's self-initiated activities at early age, but omit the elements of postural assistance from the intervention as soon as the infant shows signs of neurological improvement assessed with a standardized neurological examination. Here also lies a major challenge for research: study in a systematic way the components of hands-on techniques and their potential effect on child development and parent–infant interaction.

Dosing may be critical in the effectiveness of early intervention: putatively, only relatively high dosing has an effect on the child's developmental outcome. A high dosing may be achieved in various ways: by a high frequency or a long period of programme application, or – ideally – by a combination of both. The high dosing poses challenges both to families and to professionals.[96] It is conceivable that some families are able to cope with the challenge of high dosages of specific training activities, whereas other families may profit more from an ecological approach in which they discover themselves how the principles of developmental stimulation and environmental enrichment can be implemented best in daily life.

The review did not provide sufficient information to answer the question of whether the type of brain lesion modifies the effect of early intervention. The limited evidence available on the effect of early intervention in VHR infants emphasizes the urgent need for additional studies with a strong methodological quality. Our review has discussed the many difficulties that studies in this area may encounter. Nevertheless, we think that time and tools are ready for new studies that evaluate the effect of early intervention in VHR infants. On the basis of a more general perspective and not only on the findings of our review, we suggest that intervention programmes and their evaluation use an approach including all aspects of the International Classification of Functioning, Disability and Health, Children & Youth version.[97] This means that not only is attention paid to impairments in body structure and function, and limitations in activities and participation, but also to the environment. The environment involves family empowerment and the application of assistive devices, such as adaptive seating systems and power mobility. These assistive devices may help the infant in its discovery of the world and its interaction with other people, thereby promoting cognitive and personal development.[98–101] We have summarized our suggestions for future research in Appendix S3 (online supporting information).

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SUPPORTING INFORMATION

The following additional material may be found online:

Figure S1: Inclusion and exclusion of articles found in the search strategy.

Table SI: Mallen scores: extended methodological quality assessment.

Table SII: Characteristics of the studies included in the review.

Appendix S1: Method.

Appendix S2: Results.

Appendix S3: Suggestions for future research.

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