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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

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.

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.

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.

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 [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 pre-

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 speci c 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 speci c attention – focusing on intervention during the rst 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 modi cation 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.

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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 classi cation 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]

[illegible]

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 mer9e).

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	StrongUnclearet al.

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 Bay-

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

Outcome was assessed up and until 18 months corrected

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.

[illegible]

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.

[illegible]

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

information.[32]

responsible for the developmental difference: the frequency of therapy sessions and the amount of time that families dedicated to the implementation of the intervention pro-

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 bene cial 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 speci c training activities, whereas other families may pro t 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 suf cient information to answer the question of whether the type of brain lesion modi es 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 dif culties 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 ndings of our review, we suggest that intervention programmes and their evaluation use an approach including all aspects of the International Classi cation 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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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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