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Motor Development Interventions for Preterm Infants: A Systematic Review and Meta-analysis

Anita J. Hughes, MBPsS, MSc, ATP BA (Hons),[a] Sarah A. Redsell,[b] Cris Glazebrook[a]

abstract

[AQ2] [AQ3]

CONTEXTS: Preterm infants are at an increased risk of neurodevelopmental delay. Some studies report positive intervention effects on motor outcomes, but it is currently unclear which motor activities are most effective in the short and longer term.

OBJECTIVE: The aim of the study was to identify interventions that improve the motor development of preterm infants.

DATA SOURCES: An a priori protocol was agreed upon. Seventeen electronic databases from 1980 to April 2015 and gray literature sources were searched.

STUDY SELECTION: Three reviewers screened the articles.

DATA EXTRACTION: The outcome of interest was motor skills assessment scores. All data collection and risk of bias assessments were agreed upon by the 3 reviewers.

RESULTS: Forty-two publications, which reported results from 36 trials (25 randomized controlled trials and 11 nonrandomized studies) with a total of 3484 infants, met the inclusion criteria. A meta-analysis was conducted by using standardized mean differences [AQ4] on 21 studies, with positive effects found at 3 months (1.37; 0.48–2.27), 6 months (0.34; 0.11–0.57), 12 months (0.73; 0.20–1.26), and 24 months (0.28; 0.07–0.49). At 3 months, there was a large and significant effect size for motor-specific interventions (2.00; 0.28–3.72) but not generic interventions (0.33; −0.03 to −0.69). Studies were not excluded on the basis of quality; therefore, heterogeneity was significant and the random-effects model was used.

LIMITATIONS: Incomplete or inconsistent reporting of outcome measures limited the data available for meta-analysis beyond 24 months.

CONCLUSIONS: A positive intervention effect on motor skills appears to be present up to 24 months' corrected age. There is some evidence at 3 months that interventions with specific motor components are most effective.

[a]*School of Health Sciences, University of Nottingham, Nottingham, United Kingdom; and* [b]*Anglia Ruskin University, Cambridge, United Kingdom*

Dr Hughes identified the studies, carried out the analysis, and drafted the initial manuscript; Drs Redsell and Glazebrook assessed the studies for inclusion and reviewed and revised the initial manuscript; and all authors approved the final manuscript as submitted.

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Address correspondence to Anita J. Hughes, MBPsS, MSc, ATP BA (Hons), University of Nottingham, School of Health Sciences, 12th Floor, Tower Building, University Park, Nottingham, NG7 2RD, United Kingdom. E-mail: anita.hughes@nottingham.ac.uk

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BACKGROUND

Preterm birth is categorized as extremely preterm (<28 weeks' gestation), very preterm (28 to <32 weeks' gestation), and moderate to late preterm (32 to <37 weeks' gestation), with decreasing gestational age at birth associated with increased risk of mortality and disability and greater intensity of care.[1,2] Platt[3] highlighted that preterm birth is a common worldwide issue, with an estimated 10% of all births being preterm, although the majority of these births (85%) occur after 31 weeks' gestation. Extremely and very preterm infants (<32 weeks' gestation) are at high risk of developmental delay,[4,5] but even infants who are free of major neurodevelopmental delays are still at a higher risk of poor motor outcomes, such as subtle deficits in eye-hand coordination, sensory-motor integration, manual dexterity, and gross motor skills.[6,7] If these difficulties persist, integration and performance at school can be affected, leading to lower self-esteem.[8,9] In addition, a higher risk of attention-deficit/hyperactivity disorder has been identified not only in extremely/very preterm infants or those with a very low birth weight but also in late preterm infants and those with a weight of only 1 SD below the mean.[8] This finding has additional implications for motor development, because children with attention-deficit/hyperactivity disorder symptoms were found to be overrepresented in a community sample of children with low levels of confidence in relation to physical exercise and other barriers to physical activity.[10]

[AQ5]

Interventions for Preterm Infants

A number of interventions have aimed to enhance the neurodevelopment of preterm infants and although these are predominantly focused on improving cognitive skills, the relationship between motor and cognitive development is well established.[11–13] The majority of studies initiate recruitment while the infant is in the NICU, and a number of these focus the intervention so that it is conducted solely in the NICU setting. An example of such a program is the Newborn Individualized Developmental Care and Assessment Program (NIDCAP). The NIDCAP intervention involves trained health professionals observing the infant's behavior and adapting the care provided, such as positioning the infant and/or altering the environment of the neonatal unit, such as lighting levels. Initial results from the NIDCAP program were promising, but the longer term impact is unclear.[14–18] A systematic review on NIDCAP interventions[19] concluded that the evidence for long-term positive neurodevelopmental effects or short-term medical effects is limited. This finding may reflect restricted opportunities to develop motor skills in the neonatal unit and the importance of the timing and length of intervention, given the complexity and rapidity of developmental changes that occur in the first 3 years.[20] Evidence suggests that interventions that continue beyond discharge from the neonatal unit, and those that involve parents,[21] are more likely to show benefits.[22]

Parent-Infant Interactions

There is a good rationale for involving parents in intervention delivery because mothers experience difficulties interacting with their extremely or very preterm infants.[21] Mothers may perceive their preterm infants as being too sleepy or fragile for play in the early months after discharge and are reluctant to rouse sleeping infants,[23] with the result that infants spend long periods asleep in the supine position, restricting opportunities for motor activity. Providing opportunities for time and play in the prone position is associated with better motor outcomes,[24] and guided play may also increase the confidence of the mother in handling and interacting with her preterm infant.

A recent Cochrane review[25] of early developmental intervention programs to prevent motor and cognitive impairment highlighted the impact that even a minor motor impairment can have on a child and concluded that effective activities to enhance the motor skills of preterm infants need to be identified. This review adds to the Spittle et al[25] review by identifying activities that can improve infants' motor skills, tested via randomized controlled trials (RCTs) and nonrandomized trials that commenced in the neonatal unit or on discharge from hospital. In addition, the analyses are separated according to the age of the infant at the assessment, thus enhancing the review by Spittle et al.

Objectives

The objective was to determine whether early interventions with preterm infants that are commenced in or after discharge from the neonatal unit within the first year of life improve the development of fine and gross motor skills. A further objective was to identify the components of effective interventions to inform the development of clinical guidelines for early intervention and the delivery of care programs to reduce motor delay.

Questions

[AQ6]

1. What interventions are effective in improving the motor development of preterm infants?
2. What activities are most effective in the short/medium term?

TABLE 1 Inclusion and Exclusion Criteria

	Inclusion Criteria	Exclusion Criteria
Participant	Premature infants born at <37 weeks' gestation	Full-term infants only
Intervention	Intervention that aims to enhance infants' development	No intervention
	Interventions that continue or start once the infant has been discharged from hospital	Intervention conducted only in the neonatal unit before initial hospital discharge
Comparison	Control group from premature population	Comparison group only full-term infants
Outcome	Measure of motor development at ≤5 years	No measure of motor development preschool (≤5 years)
Study design	RCTs	Review papers; no new data
	Controlled trials	Case studies or case reports
	Cohort/comparison studies	Protocol or development publications

[AQ41]

METHODS

Inclusion and Exclusion Criteria

A protocol for the selection of studies was agreed upon by using Cochrane guidance[26] criteria for health condition/population, intervention, and study design. The elements of comparison and outcome were also incorporated into the inclusion and exclusion criteria (Table 1).

All studies that included preterm infants were eligible for inclusion. Studies reporting outcomes in children >5 years of age were not included in this review. An earlier scoping search revealed limited work in the school-aged population.

Search Strategy

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A combination of approaches were incorporated to minimize bias in the review process.[27] These included a systematic search of 17 electronic databases, including "gray literature" (Table 2).

In addition, hand searches of relevant journals and conference proceedings, reviewing reference lists, and

[AQ8]

conducting author and citation searches were also done. Myers and Ment[28] suggested that when looking at outcomes for preterm infants, advances in neonatal intensive care should be taken into account, and the available treatments for preterm

[AQ9]

infants born before the 1980s need to be considered as confounding variables. The search parameters were therefore from 1980 up to and including April 2015. No other limitations were set to the search strategy, and translations were sought when the full text was not originally published in English. Search terms are shown in Supplemental Tables 8 and 9. Supplemental Table 8 uses the Lefebrve et al[29] criteria, and an example of the search strategy in shown in Supplemental Table 9.

TABLE 2 Databases Used

Electronic Databases
AMED
CINAHL
Cochrane Central Registry
Embase
ERIC
Maternity and Infant Care
Medline
PEDro
ProQuest
PsycInfo
PubMed
Science Direct
SCOPUS
Web of Knowledge
Web of Science
EThoS
OpenGrey

The articles from the initial searches (N = 1399) were screened by the first author (A.J.H.) using title and abstract. For the second round, the full texts of the 143 remaining articles were screened independently by the authors with the use of the inclusion and exclusion criteria. One hundred articles were excluded for reasons relating to 1 of the 5 PICOS elements, as shown in Fig 1, with the use of the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-analyses) statement.[30]

Data Extraction

The data extraction sheet for this review was adapted from the Centre for Review and Dissemination[27] and The Cochrane Collaboration Handbook.[26] Data were checked for appropriateness and quality by the first author and then assessed by the remaining authors. Studies were not excluded on the basis of quality and non-RCTs were included, resulting in higher heterogeneity. Therefore, a random-effects model was used for the meta-analysis.

FINDINGS

Types of Studies

The 42 remaining publications consisted of 36 trials, 5 follow-up studies[31–35] from 3 of the primary studies, and 1 study that reported different elements over 2 publications[36,37] Of the 36 trials, 25 were RCTs[36,38–61] and 11 were nonrandomized comparison trials.[62–72] Studies with follow-up data were all RCTs that reported outcome measures at different time points (6 months' to 5.5 years' corrected age [CA][31]). Duplicated data were excluded, and only the new data were included in the relevant age-based analyses. For the meta-analysis, the data were subdivided by CA of the infant, which enabled only 1 set of data for each time point to be included. In cases in which at least 2 studies reported outcome measure data at a set age, meta-analysis was conducted within RevMan 5.3 (The Nordic Cochrane Centre, Copenhagen,

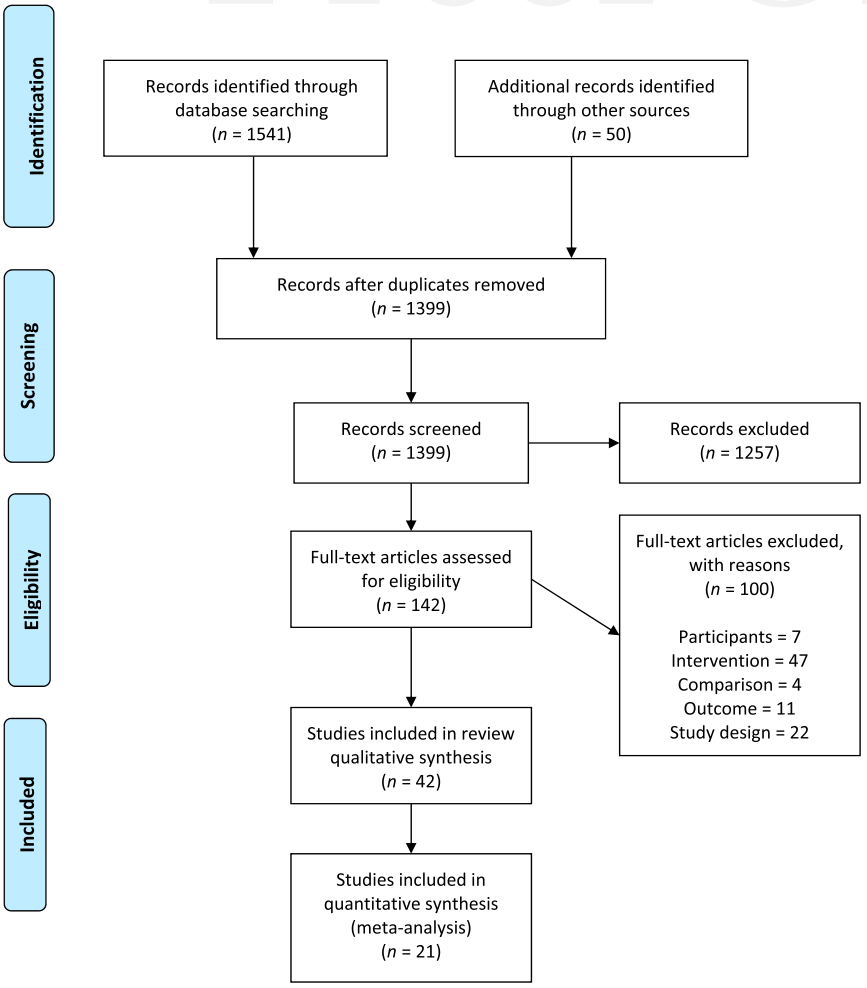


FIGURE 1
PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-analyses) flowchart of study selection process.

Denmark).[73] The data extracted were continuous: means and SDs or medians and ranges, with higher scores denoting better motor skills. Moreover the scales used to measure motor outcomes varied; therefore, standardized mean differences and random effects were used.[74] When medians and ranges were provided, the means and SDs were calculated by the first author. Heterogeneity was measured by using the I^2 test available via the Cochrane Collaboration.

Risk of bias is shown in Table 3, and the characteristics of nonrandomized studies are shown in Table 4. Both tables are displayed in the order of age at assessment.

Participants

A total of 3484 preterm infants were enrolled in the 36 studies, with *n* = 2750 participants in the 25 RCTs and an additional 734 participants included in the 11 nonrandomized studies. The sample sizes for the included studies varied from 10[64] to 285[50] participants.

The majority of RCTs recruited infants with a gestational age of <34 weeks, although the birth weight and gestational age of participants at the time of intervention varied within the studies. Almost all studies (34 of 36) recruited samples of exclusively preterm infants, with only 2 of 34 studies[41,55] including both preterm and term infants. Two studies[59,72] included an additional control group of infants born exclusively at term, but data from these groups were excluded from the review.

Those with a wide range of gestational ages and/or birth weights tended to stratify the results into early/late preterm and/or very low/low birth weight.[31–33,35,40,46–48,50,75] This method is appropriate because there is evidence that the lower the gestational age or birth weight, the higher the risk of developmental problems. However, stratification criteria were not consistently identified within the included studies. [AQ10]

Aim and Focus of the Interventions

The majority of the studies included interventions aimed at improving both the cognitive and motor development of the preterm infant. Of those 13 studies that aimed specifically at enhancing motor development, 9 were RCTs[36–38,41,42,49,50,52,55,58] and an additional 4 were nonrandomized studies.[63,64,67,68] The type of intervention varied because the focus for some of the studies was to enhance the parent-infant relationship as a means to improving infant development, whereas others were additional support or sessions with either a physiotherapist or occupational therapist. This situation resulted in the theoretical components and implementation of the intervention activities also varying. For all studies, the intervention was in addition to usual care. When categorizing by type of intervention, 8 of 13 (61.5%) studies that specifically targeted motor skills showed a significant benefit for motor skills compared with 9 of 22 (40.9%) generic interventions. [AQ11] [AQ12] [AQ13]

Initiation and Implementation of Intervention

Studies varied in the age that an intervention started, although the majority commenced while the infant was still in the neonatal unit.[32,45–47,51,55,58,61,66,69–72] Some interventions

TABLE 3 Characteristics of Included Randomised Controlled Trials

Study	Participants	Intervention	Outcome measure	Age at assessment
Lekskulchai 2001	n=111 (43 int; 41 con)	Motor Development	BSID	Term; 1; 2; 3 & 4 months
Chen 2014	n=117 (63 int; 54 con)	Multidisciplinary	BSID	2; 3; 6; 12; 18 & 24 months
Blauw-Hospers 2011	n=46 (21 int; 25 con)	Family centred physiotherapy	AIMS	3; 6 & 18 months
Tan 2004	n=60 (30 int; 30 con)	Early stage upbringing plan	GSID	3; 6; 9 & 12 months
Barrera 1986	n=59 (40 int; 19 con)	Development or Interaction	BSID	4 & 16 months
Barrera 1990			MSCA and MCDI	54 months
Cameron 2005	n=72 (34 int; 38 con)	Physiotherapy	AIMS	4 months
Heathcock 2008	n=26 (13 int; 13 con)	Motor Training	AIMS	4 months
Heathcock 2009			No set scale	
Resnick 1988	n = 41 (21 int; 20 con)	Multidisciplinary	BSID	6 & 12 months
Koldewijn 2009	n = 176 (86 int; 90 con)	IBAIP	BSID	6 months
Jeukens-Visser 2014			BSID	12 & 18 months
Koldewijn 2010			BSID	24 months
Verkerk 2012			BSID	44 months
Nurcombe 1984	n = 74 (34 int; 40 con)	Mother Infant Transaction	BSID	6 months
Ohgi 2004	n = 23 (12 int; 11 con)	Early intervention	BSID	6 months
Widmayer 1981	n = 30	Brazleton Mother & Neonatal	BSID	12 months
Bao 1999	n = 103 (52 int; 51 con)	Early intervention	BSID	18 & 24 months
Johnson 2009	n = 243 (112 int; 121 con)	Parenting	BSID	24 months
Kaaresen 2008	n = 136 (69 int; 67 con)	Mother-Infant Transaction	BSID	24 months
Spittle 2010	n = 120 (61 int; 59 con)	Preventive care programme	BSID	24 months
Spencer-Smith 2012			Movement ABC	48 months
Weindling 1996	n = 105 (51 int; 54 con)	Early physiotherapy	MAI, LbL and GSID	24 months
Wu 2014	n = 178 (120 int; 58 con)	Clinic or Home based	BSID	24 months
Kyno 2012	n = 118 (62 int; 57 con)	Mother-Infant Transaction	ASQ and MSEL	36 months
Gianni 2006	n = 38 (18 int; 18 con)	Mother-Child intervention	GSID	36 months
Johnson 2005	n = 284 (68 dev int; 84 soc int; 63 con)	Developmental or Social Support	Movement ABC	60 months
Angulo-Barroso 2013	n = 28 (15 int; 13 con)	Treadmill training	No set scale	No set age
Ma 2015	n = 285	Multidisciplinary	No set scale	No set age
Soares 2013	n = 36 (24 int; 12 con)	Practice reaching	No set scale	No set age
Yigit 2002	n = 160 (80 int; 80 con)	Early intervention	No set scale	No set age

*Several scales used. Outcome measured using: AIMS = Alberta Infant Motor Scale; ASQ = Ages and Stages; BSID = Bayley Scales of Infant Development; GSID = Griffiths Scales of Infant Development; LbL = Limb-by-Limb; Movement ABC = Movement Assessment Battery for Children; MAI = Movement Assessment of Infant; MCDi = Minnesota Child Development Inventory; MSCA = ; MSEL = Mullen Scales of Early Learning; TIMP = Test of Infant Motor Performance.

did not commence until the infant was 3[41,60,64] or 6 months' CA.[68] The intervention programs within the majority of the studies comprised activities that involved both health care professionals and parents/caregivers. In these interventions, the activities were demonstrated by the health care professionals for parents to engage in with their infant in the home environment.

Intervention Activities

[AQ14]

The majority of studies included activities such as interacting with the infant and some form of handling and positioning in the initial 2 months after birth. The positioning was adapted according to age and ability, with the amount of support decreasing as the infant's development progressed. The studies that provided the most detail about intervention activities were commenced from term to 4–6 months' CA.[41,42,49] Activities and suggested appropriate age are shown in Table 5.

Many of the studies in which the intervention activities were for ≤12 months tended to include a basic description of the type of activity included, and discriminated between fine and gross motor exercises. However, most of the studies that delivered longer term interventions provided very little detail of the activities undertaken.[39,54,58,64,72] To identify effective activities, data were extracted and the studies that reported interventions with a significant effect size ($P < .05$) were scrutinized to determine any recurring stage-appropriate activities.

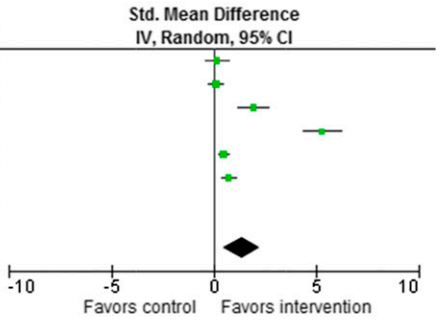
Duration of Intervention

Information regarding the duration and frequency of the intervention was described in the majority of studies and varied from 10 minutes[36,37] to sessions that lasted up to 120 minutes.[76] The number of sessions varied from 6[45] to 120.[64] The duration of the intervention program also varied: for example, lasting from birth up to term[66] as well as an intervention that commenced at 3 months' CA and lasted until the infant was 39 months' CA.[64] The majority of included studies continued the intervention beyond 3 months' CA. Most common were interventions that lasted until the infant was 6

A

Study or Subgroup	Intervention Mean	SD	Total	Control Mean	SD	Total	Weight	Std. Mean Difference IV, Random, 95% CI
Blauw-Hospers et al 2011	7.75	0.75	21	7.5	2	25	16.7%	0.16 [-0.42, 0.74]
Chen et al 2014	76	15	63	74	16	54	17.4%	0.13 [-0.24, 0.49]
Koldewijn et al 2005	92.5	6	20	79	7.5	20	15.8%	1.95 [1.18, 2.71]
Lekskulchai and Cole 2001	134.5	8.2	42	96.4	5.8	42	15.0%	5.32 [4.39, 6.24]
Li et al 2013	86.75	21.65	96	76	21.38	107	17.6%	0.50 [0.22, 0.78]
Liao et al 2009	85.3	1.2	65	80.2	9.3	75	17.5%	0.74 [0.40, 1.08]
Tan et al 2004	0	0	30	0	0	30		Not estimable
Total (95% CI)			**307**			**323**	**100.0%**	**1.37 [0.48, 2.27]**

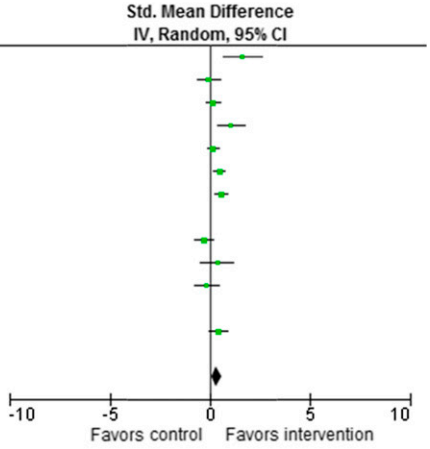
Heterogeneity: Tau² = 1.16; Chi² = 120.11, df = 5 (*P* < .00001); *I*² = 96%
Test for overall effect: Z = 3.01 (*P* = .003)



B

Study or Subgroup	Intervention Mean	SD	Total	Control Mean	SD	Total	Weight	Std. Mean Difference IV, Random, 95% CI
Alverado-Guerrero et al 2011	124	7.7	14	110	8.9	11	4.4%	1.64 [0.71, 2.57]
Blauw-Hospers et al 2011	16	4.61	21	16.25	3.75	25	7.9%	-0.06 [-0.64, 0.52]
Chen et al 2014	78	16	63	75	18	54	11.3%	0.18 [-0.19, 0.54]
Koldewijn et al 2005	94	11	20	78	18	20	6.9%	1.05 [0.39, 1.72]
Koldewijn et al 2009	97	16	86	94	16	85	12.5%	0.19 [-0.11, 0.49]
Li et al 2013	91.5	23.01	96	80.75	20.5	107	12.8%	0.49 [0.21, 0.77]
Liao et al 2009	89.3	9.4	65	84.5	7.1	75	11.8%	0.58 [0.24, 0.92]
Mazzitelli et al 2008	0	0	8	0	0	6		Not estimable
Nurcombe et al 1984	101.71	11.84	34	104.97	12.93	40	9.7%	-0.26 [-0.72, 0.20]
Ohgi et al 2004	69.8	19.2	12	63.1	13.6	11	5.2%	0.39 [-0.44, 1.21]
Resnick et al 1988	116.57	18.65	21	119.5	18.2	20	7.5%	-0.16 [-0.77, 0.46]
Tan et al 2004	0	0	30	0	0	30		Not estimable
Wu 2007	81.14	14	41	75	13	37	9.9%	0.45 [-0.00, 0.90]
Total (95% CI)			**473**			**485**	**100.0%**	**0.34 [0.11, 0.57]**

Heterogeneity: Tau² = 0.09; Chi² = 27.80, df = 10 (*P* = .002); *I*² = 64%
Test for overall effect: Z = 2.90 (*P* = .004)



C

Study or Subgroup	Intervention Mean	SD	Total	Control Mean	SD	Total	Weight	Std. Mean Difference IV, Random, 95% CI
Chen et al 2014	97	19	63	92	21	54	10.3%	0.25 [-0.12, 0.61]
Goodman et al 1985	108	18.5	40	105	13.5	40	10.1%	0.18 [-0.26, 0.62]
Jeukens-Visser et al 2014	102.8	2	84	96.6	2	79	10.0%	3.09 [2.63, 3.54]
Li et al 2013	82.75	19.34	96	77.25	20.5	107	10.5%	0.27 [-0.00, 0.55]
Liao et al 2009	93.7	8.2	65	87.2	6.8	75	10.3%	0.86 [0.52, 1.21]
Mazzitelli et al 2008	0	0	0	0	0	0		Not estimable
Ogi et al 2001	90	9.8	30	81.25	15	18	9.5%	0.72 [0.11, 1.32]
Resnick et al 1988	105.19	18.5136	21	97.55	18.0674	20	9.4%	0.41 [-0.21, 1.03]
Tan et al 2004	94.5	9	30	87	9	30	9.8%	0.82 [0.29, 1.35]
Weindling et al 1996	88	33.5	44	92	33	43	10.1%	-0.12 [-0.54, 0.30]
Widmayer and Field 1981	118	0	10	96	0	10		Not estimable
Wu 2007	98.79	11.4	43	90.12	9.48	40	10.0%	0.82 [0.37, 1.27]
Total (95% CI)			**526**			**516**	**100.0%**	**0.73 [0.20, 1.26]**

Heterogeneity: Tau² = 0.67; Chi² = 140.76, df = 9 (*P* < .00001); *I*² = 94%
Test for overall effect: Z = 2.70 (*P* = .007)

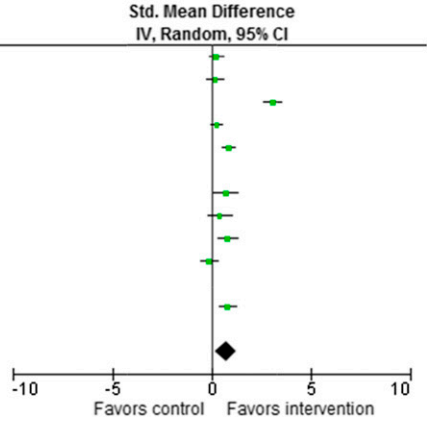


FIGURE 2
[AQ40] Forest plots for motor assessments at 3 (A), 6 (B), and 12 (C) months' CA. CI, confidence interval; IV, inverse variance.

months' CA[41,42,46,47,49,50,61,62,67,69,71] or 12 months' CA.[51,55,60,63,65,70,72,76]

Outcome Measures

A range of assessment tools were used to measure motor function, with some studies using >1 scale[41,55,70] and others assessing motor behaviors rather than using a standardized test.[37,58,64] Nineteen studies used the Bayley Scales of Infant and Toddler Development (BSID), either the first or second edition (see Tables 3 and 4). The age at assessment also varied,

[AQ15]

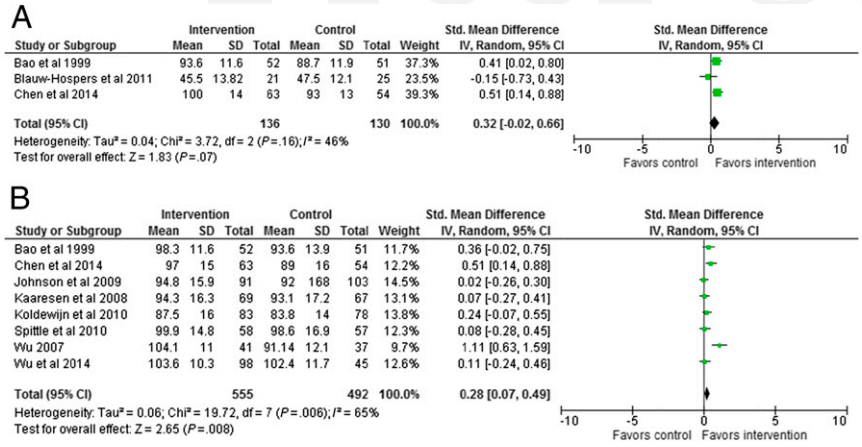


FIGURE 3

Forest plots for assessments at 18 (A) and 24 (B) months' CA. CI, confidence interval; IV, inverse variance.

although the most frequently used CA for studies that used the BSID was 6 or 24 months, followed by 12 months.

Meta-analysis

In cases in which motor assessment scores were provided at specific ages by >2 studies, meta-analysis was undertaken. Studies that measured motor function at a time point from term (40–42 weeks' gestation) to 5 years' CA were included, although most studies assessed infants up to 24 months. When sufficient intervention and control group data were provided, the effectiveness of interventions was assessed. Therefore, a meta-analysis was conducted on data at 8 different ages: term, 2 months, 3 months, 4 months, 6 months, 12 months, 18 months, and 24 months. Table 6 shows the outcome for each of the age ranges. Figures 2 and 3 show forest plots for the age ranges that contained data from at least 3 studies (Fig 2: ages 3, 6, and 12 months; Fig 3: ages 18 and 24 months).

[AQ19]

The meta-analysis revealed that interventions can enhance the motor development of preterm infants, although the effect varies over time. Significant differences were found at 3 months' CA (1.37; 0.48–2.27), 6 months' CA (0.34; 0.11–0.57), 12 months' CA (0.73; 0.20–1.26), and at 24 months' CA (0.28; 0.07–0.49), although the effect diminished over time. These time points had a range of sample sizes from 630 (3 months) to 1047 (24 months). There was no significant effect at term or at the 2-month, 4-month, and 18-month time points, but this finding may relate to the limited amount of data at those time points, because there were ≤3 studies in these analyses (n = 117–266). Data to compare motor-specific interventions with generic early intervention were limited. However, when looking at interventions with 3-month follow-up data, motor-specific interventions (N = 4)[41,49,69,70] showed a large and significant effect size at 3 months' adjusted age (2.00; 0.28–3.72), but generic interventions (N = 3)[43,54,65] showed no significant benefit for motors skills (0.33; −0.03 to 0.69). The heterogeneity of the pooled data ranged from low to high (I^2 = 36%, 99%, 96%, 99%, 64%, 94%, 46%, and 65% for term, 2 months, 3 months, 4 months, 6 months, 12 months, 18 months, and 24 months, respectively).

[AQ20]

Data Synthesis

Meta-analysis was not conducted for assessments beyond 24 months due to the limited amount of data at time points beyond this age. Seven studies (N = 704) assessed preterm infants' motor development beyond 2 years (3–5 years), 5 of which found no significant effect of the intervention on motor outcomes (N = 517).[34,35,44,48,68] Gianní et al[60] found no significant difference for the locomotor subscale of the Griffiths development assessment but found a significant difference on an eye-hand coordination subscale. Verkerk et al[33] found a significant difference at 44 months' CA on the domains of mobility of the Pediatric Evaluation of Disability Inventory–Dutch version (PEDI-NL). Of those who did not find a significant difference, Johnson et al[44] stated that there was no difference between groups at 5 years of age, but highlighted that the intervention stopped when the child was 2 years of age.

The remaining 5 studies[38,50,52,58,64] were unsuitable for meta-analysis due to either not having details of the outcome measure or age of assessment. However, 3 studies[38,50,64] found a significant difference between the intervention and control groups, in favor of the intervention.

[AQ18]

Risk of Bias

Two different assessment tools developed by the Cochrane Collaboration were used to assess risk of bias: Higgins et al's[77] criteria for risk of bias assessment was conducted on the included RCTs (Table 7) and Reeves et al's[78] guidance was used for the nonrandomized studies, where there is an increased risk of selection bias.

[AQ17]

The highest risk of bias in the RCTs was lack of blinding of participants and researchers. There was also a risk in relation to incomplete outcome data, which may reflect the duration of intervention or the stratification of participants by weight and gestational age. The potential for performance bias is known to be problematic for these

[AQ16]

TABLE 4 Characteristics of Non-Randomised Studies

Study	Participants	Intervention	Outcome measure	Age at assessment
Mathai 2001	n = 48 (25 int; 23 con)	Tactile-Kinesthetic	BNBAS	Term
Koldewijn 2005	n= 40 (20 int; 20 con)	IBAIP	BSID	3 & 6 months
Li 2013	n = 203 (96 int; 107 con)	Neurodevelopmental training	BSID	3; 6; 9 & 12 months
Liao 2009	n=140 (65 int; 75 con)	Early intervention	BSID	3; 6 & 12 months
Wu 2007	n = 83 (43 int; 40 con)	Early intervention	BSID	6; 12 & 24 months
Mazzitelli 2008	n = 14 (8int; 6 con)	Visuo-Motor Stimulation	GSID	4; 6; 8; 10 & 12 months
Alvarado-Guerrero 2011	n = 25 (14 int; 11 con)	Multidisciplinary	BSID	6 months
Goodman 1985	n = 80 (40 int; 40 con)	Home exercise	GSID	12 months
Ogi 2001	n = 48 (30 int; 18 con)	Early intervention	BSID	12 months
Salokorpi 2002	n = 126 (63 int; 63 con)	Home based Occupational therapy	MAP	48 months
Kanda 2004	n = 10 (5 int; 5 con)	Vojte method	No set scale	N/A

BSID = Bayley Scales of Infant Development; BNBAS =Brazelton Neonatal Behavioral Assessment Scale; GSID = Griffiths Scales of Infant Development; MAP = Miller Assessment for Pre-Schoolers.

TABLE 5 Example of Activities: term to four months (adapted from Lekskulchai and Cole, 2001 and Cameron et al., 2005)

Corrected Age	Activity
Term to 4 months	Midline activities in supine and alternate side-lying positions Promotion of symmetrical head turning – eye and head movement (eg support the infant and use visual/auditory stimulation to encourage eye and head movement) Facilitate upper limb reaching and midline activities in supine Facilitate hands to midline, hands to mouth, hands to feet in supine position and supported sitting position in a seat Play in supine, prone, sitting, side-lying positions Assisted kicking (eg stroking the infant's legs)
1 to 4 months	Facilitate symmetrical reaching in supine positions
2 to 4 months	Facilitate upper limb reaching and midline activities Facilitate rolling from supine to side lying to prone positions
3 to 4 months	Facilitate symmetrical reaching in prone position Facilitate reaching

[AQ21]

types of studies; therefore, detection bias is key, which for the majority of studies (RCTs and nonrandomized studies) were of low risk for detection bias, which enhances the quality of the data.

A main concern with nonrandomized studies is the risk of selection bias. For the 11 studies that were not randomized, selection onto the trial was through parent choice or systematically allocated or, in the case of the pilot study by Koldewijn et al,[69] compared with a cohort from the previous year.

Dealing With Missing Data

The majority of studies provided clear detail on the sample at recruitment or follow-up. There were instances where insufficient data were available in the publication to include in the meta-analysis and attempts were made to obtain any relevant data from the authors.

DISCUSSION

This review set out to determine whether intervention can enhance the motor development of preterm infants and to identify the most effective activities to include in a future intervention. The overall findings suggest that focused early intervention is of benefit to preterm infants, because there is a positive impact on motor skills in infants up to 24 months' CA, although the strength of the effect was reduced over time. Beyond 2 years' CA the evidence is inconclusive due to the limited amount of outcome data on motor development skills from studies. This may reflect the focus, because the majority of studies with longer follow-up tended to be general rather than motor specific, incorporating early intervention principles of being multidisciplinary and involving parenting skills and cognitive and motor skills. This lack of longer term data together with limited detail regarding the intervention activities result in challenges to developing an intervention for preterm infants that incorporates activities appropriate from birth to school age.

The RCTs and nonrandomized studies included within the review were assessed as being of acceptable quality for the main aspects of comparison group and assessment of outcome. All studies had a comparison/control group of preterm infants, and the

TABLE 6 Outcomes and effect size

Outcome/sub-group	Number of studies	Number of participants	Method	Effect
Motor score Term	2	117	Std. Mean Difference (IV, Random, 95% CI)	0.19 [-0.43, 0.67]
Motor score 2 months	2	201	Std. Mean Difference (IV, Random, 95% CI)	2.22 [-1.93, 6.37]
Motor score 3 months	7*	630	Std. Mean Difference (IV, Random, 95% CI)	1.37 [0.48, 2.27]
Motor score 4 months	3*	114	Std. Mean Difference (IV, Random, 95% CI)	2.25 [-2.71, 7.20]
Motor score 6 months	13*	958	Std. Mean Difference (IV, Random, 95% CI)	0.34 [0.11, 0.57]
Motor score 12 months	12*	1042	Std. Mean Difference (IV, Random, 95% CI)	0.73 [0.20, 1.26]
Motor score 18 months	3	266	Std. Mean Difference (IV, Random, 95% CI)	0.32 [-0.02, 0.66]
Motor score 24 months	8	1047	Std. Mean Difference (IV, Random, 95% CI)	0.28 [0.07, 0.49]

*includes studies with incomplete data

TABLE 7 Risk of bias assessment of included RCTs

Study	Random sequence generation	Allocation concealment	Blinding of participants and personnel	Blinding of outcome assessment	Incomplete outcome data	Selective reporting
Angulo-Barroso 2013	Low	Low	High	Low	Low	Low
Bao 1999	Unclear	Unclear	High	Unclear	Unclear	Low
Barrera 1986 ;1990	Unclear	Unclear	High	Low	Unclear	Unclear
Blauw-Hospers 2011	Unclear	Unclear	High	Low	Low	Unclear
Cameron 2005	Low	High	High	Low	Unclear	Unclear
Chen 2014	Low	Unclear	High	Unclear	Unclear	Unclear
Gianni 2006	Unclear	Unclear	High	Low	Low	Unclear
Heathcock 2008; 2009	Unclear	Unclear	High	Low	Unclear	Unclear
Johnson 2005	Low	Low	Unclear	Low	Low	Unclear
Johnson 2009	Unclear	Low	Unclear	Low	Unclear	Low
Kaaresen 2008	Low	Low	High	Low	Low	Unclear
Koldewijn 2009; 2010; 2012;2014	Low	Low	High	Low	Low	Unclear
Kyno 2012	Low	Unclear	High	Unclear	Low	Unclear
Lekskulchai 2001	Low	Unclear	High	Low	Low	Unclear
Ma 2015	Low	Low	High	Low	Unclear	Unclear
Nurcombe 1984	Low	Low	High	Low	Unclear	Unclear
Ohgi 2004	Low	Unclear	High	Unclear	Unclear	Unclear
Resnick 1988	Unclear	Unclear	High	Low	Unclear	Unclear
Soares 2013	Low	Unclear	Unclear	Low	High	Unclear
Spittle 2010; 2012	Low	Low	Unclear	Low	Low	Unclear
Tan 2004	Unclear	Unclear	High	Low	Unclear	Unclear
Weindling 1996	Low	Low	High	Low	Unclear	Unclear
Widmayer 1981	Unclear	Unclear	Unclear	Low	High	Unclear
Wu 2014	Low	Low	Unclear	Low	Low	Unclear
Yigit 2002	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear

majority had an assessment of the infants conducted by researchers who were unaware of group allocation. The outcome measure for this review was motor activity, and most studies used a validated development scale, of which the most frequently used was an edition of the BSID (Tables 4 and 5). Several of the studies did not use a validated scale and instead looked at age when the infant either lost or gained a particular motor behavior, such as walking.

This review focused particularly on motor development interventions as a means of ascertaining the types of activities that are most effective and to obtain information on any longer term effects. To date, there has been a stronger focus on interventions aimed at improving cognitive function, because subsequent education performance was deemed reliant on mental processing.[13] However, the interrelatedness of motor and cognitive development is clearly established,[12,79] and motor skills are a proven indicator of future math and reading success.[13]

This review attempted to add to the available data by analyzing findings at a specific CA, rather than combine them as in previous reviews,[25,80] thus allowing for potential continual effectiveness to be explored. The main trend was for a positive effect up to 24 months' CA. The time points of <24 months that were analyzed but showed no significant differences were most likely due to limited data being available. Studies that conducted

assessments at several time points were included, but duplicate data were removed. Koldewijn et al[33] consistently found a significant difference with their intervention group up to 42 months' CA. However, not enough data were available from the studies assessing beyond 24 months to conduct meta-analysis.

Identifying Activities

Orton et al found that significant levels of heterogeneity when pooling outcomes made it problematic to assess the intervention activities that were most beneficial. Despite a similar issue for this review, the number of studies included and the inclusion of nonrandomized studies ensured that some general activities and movements that were common between studies could be identified, and their effectiveness assessed, especially from birth to 6 months' CA. These included providing opportunities for movement in supine, prone, and side-lying positions with appropriate support, and facilitating hands to midline in a variety of supported positions. This is important because the most recent update of the Cochrane review on intervention programs in preterm infants[25] emphasized the need to identify effective early development interventions.

Conducting the Activities

The findings suggest that parenting interventions implemented by health care professionals have positive effects on motor skills. Providing mothers with advice and ideas of ways of interacting with their infant may help reduce the perception of preterm infants as too fragile for play in the early months after discharge.[81] Parents may have more confidence to, for example, provide opportunities for play in the prone position, which is associated with better motor outcomes. There is evidence that interventions that specifically target the infant's motor development produce substantial benefits for motor skills, at least in the short term. Nearly two-thirds of studies of motor-specific inventions produced significant effects compared with 40% of generic interventions.

Strengths and Limitations

There were limitations in relation to obtaining complete data to include in the meta-analysis, because despite attempts to obtain data, only published data were available. However, wherever possible, data were incorporated into the review via qualitative data synthesis. The strengths of the process include citation searches for authors of dissertations and theses and translation of studies not published in English. In addition, the number of duplications during the search indicates that an exhaustive search of the databases was conducted. Despite issues of potential bias, especially with including nonrandomized studies, the included trials were all of an acceptable quality for inclusion in the review. This is mainly because the majority of motor skill assessments were conducted by trained professionals, who were unaware of the group allocation of the infant being assessed.

CONCLUSIONS

The findings of the review suggest that interventions that are continued beyond the period of neonatal care can have an impact on the motor development of preterm infants, with strongest effects noted before 6 months of age, particularly where interventions specifically targeted motor skills. Stage-appropriate activities for the first 6 months and some additional activities at ~6 to 12 months' CA were identified. However, it is important that future studies provide clearer details of intervention activities to enable replication, which would help in identifying effective activities that could be used to prevent poor motor skills and developmental coordination disorder. Data on the length of interventions and long-term impact are also needed to assess if positive outcomes can be maintained beyond 24 months.

ABBREVIATIONS

BSID: Bayley Scales of Infant and Toddler Development
CA: corrected age
NIDCAP: Newborn Individualized Developmental Care and Assessment Program
RCT: randomized controlled trial

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AUTHOR QUERIES

[AQ1]: **Please verify author names, academic degrees, and affiliations and add department name for "Anglia Ruskin University". Please add highest academic degrees for second and third authors. Also should third author's first name be Cris or Cristine (as per the pdf)? Please also verify accuracy of courtesy titles (Dr) in the contributors' statements.**

[AQ2]: Please verify corresponding author's contact information.

[AQ3]: Please confirm whether any funding for this research was provided by the National Institutes of Health (NIH).If so, provide relevant grant information.

[AQ4]: Au: Please clarify what the values in parentheses represent here and in text (eg, odds ratio; 95% confidence interval)?

[AQ5]: The use of "This" alone here is ambiguous. Please verify "This finding" or provide another noun for clarity.

[AQ6]: **Au: Can an introductory sentence be added in the Questions section to introduce the list?**

[AQ7]: Au: Please confirm or amend edits for wording in sentence beginning "Search terms are shown ...."

[AQ8]: Au: "A.J.H." correct as added?

[AQ9]: Au: Please spell out PICOS.

[AQ10]: The use of "this" alone here is ambiguous. Please verify "This method" or provide another noun for clarity.

[AQ11]: Au: There appear to be citations for 10 studies here. Please check.

[AQ12]: Au: Please clarify " others were" here (eg, others focused on).

[AQ13]: The use of "this" alone here is ambiguous. Please verify "This situation" or provide another noun for clarity.

[AQ14]: Au: Please confirm or amend edits for wording in statement beginning "for example, lasting from birth up to term ...."

[AQ15]: Au: Please confirm or amend definition of BSID as edited.

[AQ16]: Au: Please clarify the values in parentheses (eg, odds ratios; 95% confidence intervals).

[AQ17]: AU: "−0.03 to 0.69" correct as set? Or should 0.69 also be a negative number?

[AQ18]: Au: " The remaining 5 studies ..." ok as edited?

[AQ19]: Au : Because single subheadings are not allowed within larger sections, the heading "Assessment of risk of bias" was deleted here.

[AQ20]: Au: "gestational age" ok as edited?

[AQ21]: The use of "This" alone here is ambiguous. Please provide a noun after "This" for clarity.

[AQ22]: Au: Reference 33 does not correspond to first author "Koldewijn". Please correct.

[AQ23]: Au: Please add citation for "Orton et al".

[AQ24]: Au: "complete data" ok as edited?

[AQ25]: The use of "This" alone here is ambiguous. Please provide a noun after "This" for clarity.

[AQ26]: AU: Clarify editor/author names (W D, R L, D K) in reference 12 and provide page range of cited chapter.

[AQ27]: Medline indexes "J Reprod Infant Psychol" but cannot find a listing for reference 23 "Nicolaou, Marlow, Glazebrook, 2009". Please check the reference for accuracy.

[AQ28]: Au: Reference 26: Provide publisher's location, or if this is an online site, provide URL and date on which the Web site was accessed. See also reference 78.

[AQ29]: Au: Reference 29: Clarify authors' last names/first name initials for " E M, J G" and editor "S G". Please also provide publisher's location or, if online, URL and date accessed.

[AQ30]: Medline cannot find the journal "Top Early Child Spec Educ" (in reference 35 "Barrera, Kitching, Cunningham, Doucet, Rosenbaum, 1990"). Please check the journal name.

[AQ31]: Medline cannot find the journal "Chinese Journal of Clinical Rehabilitation." (in reference 54 "Tan, Tong, Huang, Deng, Hu, Zhang, 2004"). Please check the journal name.

[AQ32]: Medline indexes "Neurosci Med" but cannot find a listing for reference 62 "Alvarado-Guerrero, Poblano, Marosi, Corsi-Cabrera, Otero-Ojeda, 2011". Please check the reference for accuracy. Please also provide issue number.

[AQ33]: Au: References 65 and 71: Please indicate the original language, in brackets, after the article title.

AUTHOR: Read proofs carefully. This is your ONLY opportunity to make changes.
NO further alterations will be allowed after this point.

AUTHOR QUERIES

[AQ34]: Au: Reference 67: Please clarify journal volume/issue numbers and page range.

[AQ35]: Medline cannot find the journal "Chinese Journal of Rehabilitation Medicine." (in references 70 and 72). Please check the journal name.

[AQ36]: Au: Original Reference 77 was a duplicate of reference 69 and has been deleted. Please check renumbering.

[AQ37]: Au: Please clarify page range in reference 76.

[AQ38]: Please provide issue number in journal references. (in reference 77 "Higgins, Altman, Gotzsche, et al, 2011").

[AQ39]: Au: Please define AMED in Supplemental Table 9 footnote.

[AQ40]: Au: Figures 2 and 3. Please check legends as edited. Please also check accuracy of author names listed for the studies.

[AQ41]: Au: Table 2: Check table title as edited.

Supplemental Information

SUPPLEMENTAL TABLE 8 Search Terms Using Lefebvre et al (2011) Criteria

Term Category	Search Terms Used
Health condition/ population	"premature infant*/infant premature/preterm/prematurity"
Intervention	"motor; development/skill/performance/activity/movement"
Study design	"randomi*ed controlled trial*/controlled/comparative/intervention study/trial"

SUPPLEMENTAL TABLE 9 Search Strategy: Examples From AMED Database

Item	Searches	Results
S1	premature infant*.mp or infant premature/	146
S2	preterm.mp	204
S3	prematurity.mp	25
S4	S1 or S2 or S3	284
S5	motor development.mp	223
S6	motor skill*	1076
S7	Motor activity	1272
S8	Motor performance.mp	486
S9	Movement	4664
S10	S5 or S6 or S7 or S8 or S9	7208
S11	Randomized controlled trial*/or randomized controlled trial.mp	2199
S12	Controlled trial*	3338
S13	Trial*	8451
S14	Comparative study	4749
S15	Intervention study	266
S16	S11 or S12 or S13 or S14 or S15	13 827
S17	S4 and S10	66
S18	S16 and S17	9

AMED, XXXX.