A regional follow-up study at two years of age in extremely preterm and very preterm infants.

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CHAPTER 8

Developmental outcome at 18 and 24 months of age in very preterm children: a cohort study from 1996 to 1997

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Abstract

Objective: To determine the effect of prematurity (gestational age (GA) < 32 weeks) on developmental outcome at the corrected age of 18 and 24 months in a regionally defined, prospective cohort study.

Study design: The Leiden Follow-Up Project on Prematurity includes all live-born infants of < 32 wks GA, born in 1996/1997 in 3 Dutch health regions (n=266). Mental and psychomotor developmental indices (MDI, PDI) were determined with the Bayley Scales of Infant Development I: ≥ -1 SDS: normal, -2 to -1 SDS: moderate delay and < -2 SDS: severe delay.

Results: At 18 months 168 (71%) and at 24 months 151 children (64%) of 235 survivors were assessed. Moderate to severely delayed mental and/or psychomotor development occurred in 40% of the children at both ages. Children lost to follow-up were of lower socio-economic status and more frequently of non-Dutch origin. Since non-Dutch origin negatively affected outcome at both test ages, availability of the data of these children would probably have worsened the outcome. Postnatal treatment with dexamethasone was associated with an increased risk of delayed development. Other independent predictors of delayed development were bronchopulmonary dysplasia at 18 months and ethnicity, maternal age at birth, GA, birthweight and gender at 24 months. After adjustment for these other predictors of delayed development, the mean PDI of dexamethasone-treated infants was 16.1 points lower than that of non-treated infants at 18 months (p=0.03) and 12.7 points lower at 24 months (p=0.04).

Conclusions: At 18 and 24 months corrected age, 40 percent of the very prematurely born children had both delayed mental and/or psychomotor development. Treatment with dexamethasone postnatally was a major risk factor for delayed (psychomotor) development.

Introduction

Advances in neonatology have led to an increased survival of very preterm infants.[1] To evaluate the effect of these ongoing changes in neonatal care on morbidity, the neurodevelopmental outcome of these infants is closely monitored.

Previous studies have shown that preterm infants, especially those with chronic lung disease or extensive intraventricular haemorrhage, are at greater risk of developmental disorders.[2-4] Apart from these medical risk factors, social risk factors, such as low socioeconomic status of the parents, may also have negative effects on children's development.[3-5]

In this paper we report on the developmental outcome at 18 and 24 months corrected age of a recent, regional, Dutch cohort of very preterm infants. We will compare the findings to the Dutch reference norms. Furthermore, the influence of both medical and social risk factors on developmental outcome will be examined. In view of recent findings suggesting that postnatal treatment with dexamethasone may have adverse effects on neurodevelopmental outcome[6-8], close attention will be paid to the possible influence of this treatment on developmental outcome.

Development was assessed at both 18 and 24 months to see if a developmental profile could be detected and if so, which medical and/or social factors could explain this difference.

Patients and methods

Patients

The Leiden Follow-Up Project on Prematurity, a regional, prospective study, includes all liveborn infants less than 32 weeks gestational age (GA) from the Dutch health regions Leiden, The Hague and Delft, born in 1996 or 1997 (n=266). All infants $\geq$ 24 weeks GA were actively resuscitated at birth.

The three Dutch health regions used in the study are situated in the Dutch province Zuid-Holland. In the years 1996/1997 this province had 3.34 million inhabitants on a total of 15.53 million people living in the entire Netherlands. With 21% of the total Dutch population living in this province, it is a reasonably

densely populated region. The three studied health regions (The Hague, Delft and Leiden) together had 1.43 million inhabitants at that time, which is 43% of the total inhabitants of the province of Zuid-Holland and 9% of the entire Dutch population. The health region The Hague had the most inhabitants: 49% of the 1.4 million, versus 33% in the health region Leiden and 19% in the health region Delft.

The total number of live births in the Netherlands was 191.000 in the years 1996/1997, 41.250 in the province Zuid-Holland (21% of the total) and 17.450 (9% of total, 43% of live-births in Zuid-Holland) in the three studied health regions. Forty-five percent of the live-births in the studied health regions occurred in the region The Hague, 35% in Leiden and 20% in Delft.

Follow-up of the infants included physical examinations and assessment of neuromotor development by a paediatrician at term and at the corrected ages of 12 and 24 months. Mental and psychomotor development was assessed at 18 and 24 months corrected age by 6 developmental psychologists, who were 'blind' to the child's medical history.

The study was approved by the Ethics Committee of the Leiden University Medical Center. Parental informed consent was obtained.
In this work, all mentioned ages hereafter are corrected for prematurity.

Instruments

Mental and psychomotor development were assessed using the Dutch version of the Bayley Scales of Infant Development I.[9;10] These scales have a population-mean of 100 and a standard deviation of 16. The Mental and Psychomotor Developmental Index (MDI, PDI) range between 51 and 149. If raw test scores were either so low or so high that developmental indices could not be determined, index-scores of 50 and 150, respectively, were given.

An MDI or PDI $\geq$ 84 ($\geq$ -1 SD) was considered normal, an MDI or PDI between 68 and 84 (-2 to -1 SD) was considered as moderate delay and $<$ 68 ($<$ -2 SD) as severe delay.

In accordance with the Bayley manual, a difference of 19 and 15 points at 18 and 24 months respectively between MDI and PDI was considered to be significant ($p < 0.05$). Such a difference was defined as dysharmonic.

For mental development a difference of 14 points between the MDI at 18 and 24 months was considered significant, for psychomotor development a difference of 20 points.

Medical factors

Medical factors were collected on precoded forms. Data collected included: obstetric history, mode of delivery, GA, gender, birthweight, small for GA (birthweight < P10)[11], complications during admission like hypotension (at least twice a mean blood pressure < 30 mmHg, measured oscillometrically [Dynamap] or intra-arterially), bronchopulmonary dysplasia (BPD, supplemental oxygen need at 36 weeks postmenstrual age)[12], intraventricular haemorrhage (IVH)[13], cystic periventricular leucomalacia (PVL)[14] and treatment with dexamethasone in the postnatal period.

Dexamethasone was given with an initial dose of 0.5 mg/kg and tapered over 42 days to 0.1 mg/kg. However, duration of treatment depended on the clinical condition of the child and varied between 5 and 60 days (mean 31 days).

Neurological outcome at term (Prechtl)[15] and at 2 years of age (Hempel)[16] was defined as normal, mildly or definitely abnormal. Definitely abnormal means the presence of a full-blown neurological syndrome like asymmetry, general hyper/hypotonia, hyper/hypokinesia; mildly abnormal the presence of only part of such a syndrome.

Social factors

Socioeconomic status (SES) was determined by the level of education of each parent. A score of 1 was given if the parent's educational level was low (elementary school, lower level secundary or professional education), a score of 2 for an average educational level (medium level secundary or professional education) and a score of 3 for higher levels of education (high level professional education, university).[17]

Ethnicity was defined as Dutch or non-Dutch origin (mostly Turkish, Moroccan or Surinamese origin).

Statistical analysis

The mean MDI and PDI scores of the study population were compared with the reference population using a one sample *t*-test. The observed percentages of children with normal, moderately or severely delayed mental and psychomotor development were compared with the expected values using the chi-square test. ANOVA and bivariate correlation (Pearson/Spearman) were used for univariate analyses.

Multiple linear regression analysis, with the continuous MDI and PDI scores

as dependent variables, was used to estimate the predictive value of medical and social factors on mental and psychomotor outcome. Ethnicity, SES, gender, use of glucocorticosteroids antenatally, maternal age at birth, GA, birthweight (percentile according to GA), extra-uterine transportation, hypotension, IVH, PVL, BPD and treatment with dexamethasone in the postnatal period were the independent predictors. The goodness-of-fit of this model was evaluated by inspection of the histogram of the residuals and scatterplots of the residuals versus covariates.
P-values < 0.05 were considered significant.

Results

The study included 266 children, 92% of eligible infants born in 1996 and 1997 (97% of eligible infants in 1996 and 88% of eligible infants in 1997). Thirty (11%) of the 266 children died, 28 in the neonatal period and 2 more before the age of one year. Treatment was withdrawn in 15 of these infants because it was considered to be medically futile.

In this study, a total of 163 (61%) children were born in hospitals with a neonatal intensive care unit ([NICU], tertiary referral centers), 103 (39%) in hospitals without a NICU. The patient characteristics of the entire cohort are presented in Table 1.

One child was excluded from the analyses because of Down's syndrome. Of the remaining 235 survivors, 168 children (71%) were assessed at 18 months and 151 (64%) at 24 months. Three infants had such severe disabilities that scores of 50 were given for both mental and motor development without actual testing. One child could not be tested due to blindness.
Reasons for the loss-to-follow-up were families moving to other cities or countries and parental refusal to co-operate. Birth characteristics (GA, birthweight, gender) and incidences of respiratory distress syndrome, oxygen dependence at 28 days, BPD, hypotension, IVH, PVL and postnatal treatment with dexamethasone of the lost-to-follow-up-group did not differ from those of the study group. Parents of the children of the lost-to-follow-up-group were of lower SES and were more frequently of non-Dutch origin.

Table 1. Characteristics of the LFUPP-cohort (n=266)

Antenatal steroids, % (n)	75 (182)
Male gender, % (n)	55 (147)
Gestational age:	
weeks, mean (SD)	29.2 (2.1)
24-26 weeks, % (n)	17 (46)
27-28 weeks, % (n)	23 (61)
29-31 weeks, % (n)	60 (159)
Birthweight, mean (SD)	1250 (383)
Small for GA (birthweight <P10), % (n)	13 (33)
Apgar 5 min, mean (SD)	7.7 (1.8)
Extra-uterine transport, % (n)	35 (93)
Hypotension*, % (n)	34 (98)
O2 at 28 days, % (n)	26 (67)
Bronchopulmonary dysplasia**, % (n)	19 (49)
Mechanical ventilation, days, mean (SD)	7.2 (9.3)
Dexamethasone postnatally, % (n)	17 (45)
Intraventricular haemorrhage, % (n)	
none	74 (190)
grade 1-2	18 (48)
grade 3-4	8 (20)
Periventricular leucomalacia (cystic), % (n)	3 (8)
In hospital mortality, % (n)	11 (29)
Dutch origin, % (n)	75 (167)
Level of education mother, % (n)	
high	29 (60)
average	50 (105)
low	21 (44)
Maternal age at birth, yrs, mean (SD)	30.5 (5.6)

LFUPP: Leiden Follow-Up Project on Prematurity; SD: standard deviation
GA: gestational age; * at least twice a mean blood pressure < 30 mmHg;
** O2 at 36 weeks postmenstrual age

Developmental outcome

The results of the assessments at 18 and 24 months of age are presented in Table 2 for MDI and PDI separately.

Mean MDI at 18 and 24 months and PDI at 24 months were significantly lower than 100. At both ages, the percentages of children with normal, moderately delayed and severely delayed development differed ($p<0.001$) from those in the reference population. Delayed development, especially more severely delayed development, occurred more often among the very preterm infants than in the reference population.

At 18 and 24 months of age, both mental and psychomotor development were normal in 60% of the children (98 and 85 children, respectively). Mental and psychomotor development were severely delayed in 11 children (7%) at 18 and 9 children (6%) at 24 months. In the remaining 33-34% of children at least one of the parameters was abnormal.

Table 2. Mental and psychomotor development at 18 and 24 months corrected age

	Mean (SD)	**Range**	**Normal** % (n)	**Moderate delay** % (n)	**Severe delay** % (n)	**Total** n
18 months (mean 18.0, SD 1.3)						
MDI	95.1 (20.7)★	50-142	**73** (121)	**18** (30)	**9** (15)	166★★
PDI	95.7 (25.8)★	50-150	**71** (116)	**11** (18)	**18** (29)	163★★
24 months (mean 24.8, SD 1.6)						
MDI	97.3 (24.8)	50-150	**73** (107)	**12** (18)	**15** (21)	146★★
PDI	95.8 (21.7)★	50-150	**70** (100)	**22** (32)	**8** (12)	144★★
Reference population	100 (16)		**84**	**13.5**	**2.5**	

SD: standard deviation, MDI: mental developmental index, PDI: psychomotor developmental index, Normal: ≥ -1 SD, Moderate delay: -2 to -1 SD, Severe delay: < -2 SD.

★significantly below the test mean of 100, p=0.003 for MDI and p=0.03 for PDI at 18 months, p=0.02 for PDI at 24 months.

★★MDI and PDI could not be determined in respectively 2 and 5 children at 18 months and 5 and 7 children at 24 months.

Intra-individual differences

Significant differences between MDI and PDI at 18 months were found in 59 of 163 children (36%): 31 had better mental development and 28 had better psychomotor development. At 24 months, differences existed in 64 of 142 (45%) children: 33 had better mental development and 31 had better psychomotor development. These intra-individual differences exceeded the expected 5% of children with a dysharmonic profile in the reference population ($p<0.001$).

Changes between the two test ages

Although the mean MDI and PDI at 18 months did not differ from those at 24 months, significant changes between MDI scores at 18 and 24 months were found in 67 of 136 tested infants (49%): 32 infants had a worse mental outcome and 35 children had a better mental outcome at 24 months of age. Changes in PDI scores existed in 45 of 132 tested infants (34%): 23 infants had a worse psychomotor outcome and 22 children had a better psychomotor outcome at 24 months of age. These changes differed ($p<0.001$) from the expected 5% of children with a significant improvement or deterioration in the reference population.

Association between medical factors and developmental outcome

Higher GA was associated with an increase in MDI scores at 18 and 24 months (correlation coefficient $r = 0.29$, $p<0.001$ and $r = 0.19$, $p=0.02$). PDI scores also increased with higher GA at 18 and 24 months ($r = 0.25$, $p=0.001$ and $r = 0.26$, $p=0.001$).

The association of other medical factors with developmental outcome is shown in Table 3 (18 months) and 4 (24 months). Male children had lower MDI scores at both ages and lower PDI scores at 24 months than female children, infants with hypotension in the neonatal period had lower PDI scores at 18 months than those without hypotension. Both MDI and PDI scores were lower at 18 and 24 months in infants with PVL, oxygen dependence at 28 days, BPD, postnatal dexamethasone treatment and neurological abnormalities at term or at 2 years of age.

Better mental than psychomotor development or vice versa at 18 or 24 months of age was not associated with any of the medical factors listed in Tables 3 and 4.

No associations were found between the medical factors and the mental and psychomotor outcome of children whose outcome significantly improved or deteriorated between the age of 18 and 24 months.

Table 3. Mental and psychomotor development at 18 months corrected age in relation to medical factors

	MDI mean; SD (n)			PDI mean; SD (n)*		
Medical factor	**+**	**-**	**p****	**+**	**-**	**p****
antenatal steroids	94; 20 (108)	98; 23 (44)	0.2	95; 24 (107)	98; 28 (43)	0.5
GA < 27 weeks	81; 17 (20)	97; 20 (146)	0.001	82; 27	98; 25 (143)	0.01
birthweight < P10 (SGA)	94; 20 (22)	95; 21 (143)	0.7	99; 19 (21)	95; 27 (141)	0.5
gender: male	91; 21 (93)	100; 19 (73)	0.005	93; 25 (90)	99; 27	0.1
extra-uterine transport	94; 22 (57)	96; 20 (109)	0.5	100; 24 (56)	93; 27 (107)	0.1
hypotension#	92; 20 (56)	97; 21 (108)	0.1	89; 26 (54)	100; 25 (107)	0.01
IVH grade 3-4	95; 25 (11)	95; 20 (151)	0.9	88; 31	97; 25 (148)	0.3
PVL (cystic)	70; 18 (6)	96; 20 (157)	0.002	70; 22	97; 25 (154)	0.01
O2 at 28 days	86; 21 (50)	99; 19 (113)	<0.001	83; 26	102; 23 (110)	<0.001
BPD (O2 at 36 wks)	82; 20 (37)	99;20 (126)	<0.001	81; 27	101; 23 (123)	<0.001
dexamethasone postnatally	81; 17 (27)	98; 20 (138)	<0001	76; 23	99; 25 (135)	<0.001
neurological abnormalities at term	91; 22 (78)	99; 19 (87)	0.02	89; 27 (76)	102; 23 (86)	0.001
neurological abnormalities at 24 months	81; 20 (48)	101; 19 (104)	<0.001	78; 26	103; 22 (102)	<0.001

*numbers are only mentioned again if different from the MDI-number,
** *t*- test, # hypotension: at least twice a mean blood pressure < 30 mmHg,
MDI: mental developmental index; PDI: psychomotor developmental index; SD: standard deviation; GA: gestational age; SGA: small for gestational age; IVH: intraventricular haemorrhage; PVL: periventricular leucomalacia; BPD: bronchopulmonary dysplasia

Table 4. Mental and psychomotor development at 24 months corrected age in relation to medical factors

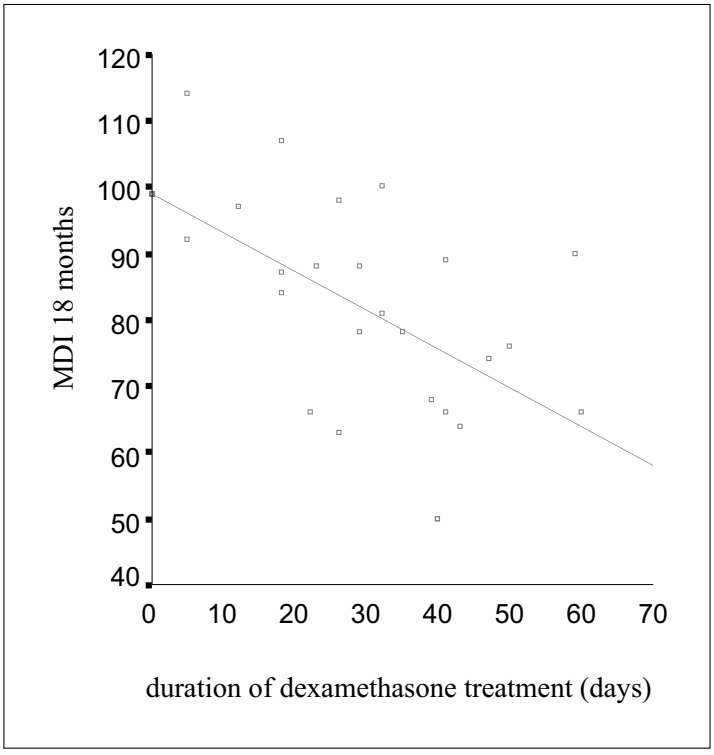
	MDI mean; SD (n)			PDI mean; SD (n)*		
Medical factor	**+**	**-**	**p****	**+**	**-**	**p****
antenatal steroids	97; 25 (100)	97; 27 (37)	0.9	96; 21 (985)	96; 23	0.9
GA < 27 weeks	91; 24 (21)	98; 25 (125)	0.2	87; 21 (22)	97; 21 (122)	0.03
birthweight < P10 (SGA)	90; 28 (22)	99; 24 (123)	0.1	93; 21	96; 22 (121)	0.4
gender: male	93; 26 (85)	103; 23 (61)	0.02	93; 23 (83)	100; 18	0.04
extra-uterine transport	91; 27 (47)	100; 23 (99)	0.04	96; 24	96; 21 (97)	0.9
hypotension#	95; 24 (50)	99; 25 (95)	0.4	93; 21	98; 22 (93)	0.2
IVH grade 3-4	90; 32 (10)	98; 24 (135)	0.3	83; 26	97; 21 (133)	0.05
PVL (cystic)	69; 21 (5)	98; 25 (140)	0.01	78; 23 (6)	97; 22 (137)	0.04
O2 at 28 days	90; 24 (46)	101; 24 (98)	0.009	86; 20 (47)	101; 21 (95)	<0.001
BPD (O2 at 36 wks)	88; 25 (36)	101; 24 (108)	0.006	87; 21(37)	99; 21 (105)	0.003
dexamethasone postnatally	84; 26 (25)	100; 24 (119)	0.003	82; 21 (26)	99; 21 (116)	<0.001
neurological abnormalities at term	94; 27 (73)	100; 23 (72)	0.2	92; 21 (72)	100; 21 (71)	0.02
neurological abnormalities at 24 months	82; 27 (45)	104; 21 (92)	<0.001	79; 22 (46)	104; 16 (89)	<0.001

*numbers are only mentioned again if different from the MDI-number,
**t- test, # hypotension: at least twice a mean blood pressure < 30 mmHg.
MDI: mental developmental index; PDI: psychomotor developmental index; SD: standard deviation; GA: gestational age; SGA: small for gestational age; IVH: intraventricular haemorrhage; PVL: periventricular leucomalacia; BPD: bronchopulmonary dysplasia

Treatment with dexamethasone in the postnatal period

Twenty-seven infants in the assessed group were treated with dexamethasone postnatally (16%). Treatment was started at a mean age of 19 days (range 5-42), the mean duration of treatment was 31 days (range 5-60). Treatment with dexamethasone was univariately associated with delayed mental and psychomotor development at 18 and at 24 months of age (Tables 3 and 4) and the duration of treatment was associated with delayed mental development at 18 months (r = -0.6, p=0.006; Fig. 1).

Figure 1. MDI-scores at 18 months in relation to duration of dexamethasone treatment postnatally (MDI: Mental Developmental Index)



Association between social factors and developmental outcome

Both ethnicity and SES were divided into three groups. At 18 months of age the percentage of parents of Dutch origin was 80%, while 15% of the parents were of non-Dutch origin and 5% of the children had one parent of Dutch and one of non-Dutch origin.

Twenty-two percent of the mothers and 27% of the fathers had low levels of education, 56% and 39% average levels and 22% and 33% had high levels of education. The percentages found at 24 months were comparable.

Average maternal age at birth was 30.6 years (SD 4.7), which is comparable to the average age at birth of Dutch women of 30.4 years in those years.

Children of Dutch origin had higher MDIs at both 18 and 24 months than children of non-Dutch origin: mean MDI at 18 months was 97 vs. 88 for the non-Dutch children (p=0.04), at 24 months the corresponding numbers were 101 and 84 (p=0.002).

Higher maternal age at birth was associated with better mental development at 24 months *(r* = 0.19, p=0.03). Educational level of the parents was not associated with development at 18 or 24 months.

Higher educational levels of the mother and higher maternal age at birth were associated with improvement in mental development between 18 and 24 months (*r* = 0.18, p=0.004 and *r* = 0.26, p=0.003, respectively).

Multivariate analysis

Univariately, we found that lower maternal age at birth, non-Dutch origin, lower GA, male gender, hypotension, oxygen dependence at 28 days, BPD, postnatal treatment with dexamethasone, PVL and neurological abnormalities at term or 2 years were associated with delayed mental and/or psychomotor development at 18 and/or 24 months. In order to disentangle these univariate effects, a multiple regression analysis with stepwise selection was done. BPD was the only independent predictor for delayed mental development at 18 months. BPD and postnatal treatment with dexamethasone were the independent predictors for delayed psychomotor development at this age. Birthweight and postnatal treatment with dexamethasone were the only independent predictors for delayed psychomotor development at 24 months; ethnicity, maternal age at birth and gender were predictive of delayed mental development as well.

Since postnatal dexamethasone treatment was associated with several of the covariates, we repeated the stepwise analysis without dexamethasone to identify

the confounders of the dexamethasone effect. These confounders were BPD at 18 months and ethnicity, maternal age, birthweight and gender at 24 months for delayed mental development. For delayed psychomotor development these were BPD at 18 months and birthweight at 24 months. The effects of dexamethasone after correction for these significant confounders were a 10.9 (S.E. = 6.3) lower MDI score at 18 and a 9.3 (S.E. = 6.6) lower MDI score at 24 months, and 16.1 (S.E. = 7.3) and 12.7 (S.E. = 6.1) lower PDI scores at 18 and 24 months, respectively (Table 5). When correcting further for all other predictors, the dexamethasone effects were slightly less for mental development but remained approximately the same and significant for psychomotor development (Table 5).

Table 5. Results unstandardized coefficient *(b)* of dexamethasone + S.E. and p-value of multiple linear regression analysis

	Mental Development		**Psychomotor Development**	
	18 months	**24 months**	**18 months**	**24 months**
Confounding				
univariate	-16.9 (S.E. 4.2, p<0.001)	-15.9 (S.E. 5.3, p=0.003)	-23.0 (S.E. 5.2, p<0.001)	-17.2 (S.E. 4.5, p<0.001)
adjusted for significant confounders*	-10.9 (S.E. 6.3, p=0.08)	-9.3 (S.E. 6.6, p=0.16)	-16.1 (S.E. 7.3, p=0.03)	-12.7 (S.E. 6.1, p=0.04)
adjusted for all confounders	-7.3 (S.E. 6.5, p=0.27)	-6.8 (S.E. 7.3, p=0.36)	-15.0 (S.E. 7.9, p=0.06)	-11.0 (S.E. 7.0, p=0.02)

The coefficient (*b*) represents the difference between the mean scores of infants treated and not-treated with dexamethasone postnatally. The minus sign indicates that the mean score of treated infants was lower than that of untreated infants. S.E.: standard error

* Mental development: 18 months: bronchopulmonary dysplasia (*b* =-12.3, p=0.03); 24 months: ethnicity (*b* =-11.4,p<0.001), maternal age (*b* =1.4, p=0.002), birthweight (*b* =0.19, p=0.001), gender (*b* =-10.1, p=0.02). Psychomotor development: 18 months: bronchopulmonary dysplasia (*b* =-14.2, p=0.03); 24 months: birthweight (*b* =0.12, p=0.03)

Discussion

In this study of the developmental outcome at 18 and 24 months corrected age of a cohort of very preterm infants (<32 wks GA) born in 1996/1997, we found that approximately 60% of the children had both normal mental and psychomotor development at both ages. In the remaining 40% of infants, 6-7% had both severe mental and psychomotor delay, while 33-34% had either moderate to severe mental and/or psychomotor delay.

The use of different inclusion criteria makes it difficult to compare these results with previously reported outcome-studies. Most of these studies reported outcome according to birthweight and only included extremely preterm or extremely low birthweight infants. Since the introduction of surfactant, no studies matching our intake criteria were available for comparison. Furthermore, in our study the Bayley Scales of Infant Development I (BSID-1) were used, while most other recent reports on developmental outcome use the second edition of these scales. However, since the BSID-2 was not validated yet for the Dutch population in the study-period, we had to use the first edition. Since the BSID-2 appears to give lower scores than the BSID-1[18], the results probably would have been worse if the BSID-2 could have been used.

The loss-to-follow-up with regard to the Bayley-assessment was considerable in this study. The loss-to-follow-up group differed from the study group in both ethnic origin (more non-Dutch parents in the lost group) and SES (lower educational levels of the parents). Since ethnic origin affected outcome at both test ages, availability of the data of these children would probably have worsened the outcome.

Development was assessed at 18 and 24 months to investigate if a developmental profile could be detected and if so, which medical and/or social factors could explain this difference. Significant differences in mental development between 18 and 24 months existed in 49% of the children. Except higher maternal education and age, which were associated with an improvement in mental outcome, no other social or medical factors were found which could explain this difference.
As reported in previous studies, we also found that medical factors such as lower GA, BPD and neurological abnormalities were univariately associated with delayed mental and/or psychomotor outcome.[2;4] Social factors did not play an important role at 18 months of age, but were associated with poorer outcome at 24 months of age. At this age, delayed mental development occurred more often

in children of young mothers and in children of non-Dutch origin.

The fact that social factors become more important as children grow older has been reported before.[4;19] The association between postnatal dexamethasone treatment and delayed mental and psychomotor outcome however, has been reported only recently. In a double blind randomized controlled trial O' Shea *et al.*[6] found a higher rate of cranial ultrasound abnormalities and cerebral palsy at 12 months corrected age in very low birthweight infants treated with a 42-day course of dexamethasone, but they did not find differences in MDI or PDI scores. Yeh *et al.*[8] reported a higher incidence of neuromotor dysfunction in dexamethasone-treated infants at 24 months corrected age. MDI and PDI scores in the dexamethasone treated infants did not differ from those of the control group. More recently, Shinwell *et al.*[7] reported a higher incidence of cerebral palsy and developmental delay at a mean of 53 months of age in infants treated with dexamethasone before 12 hours of age compared to infants who received placebo. Development was however not assessed with a detailed developmental test and the age at follow-up ranged from 24 to 71 months.

Although our study is not a randomized controlled trial studying the effects of dexamethasone treatment, we did find a strong association between postnatal treatment with dexamethasone and developmental delay. Treatment with dexamethasone was only given to infants with severe respiratory problems to wean them of the ventilator.The poor clinical condition of these infants may have negatively influenced their developmental outcome. Corrected for pulmonary and other perinatal and social risk factors for delayed development however, the association between dexamethasone treatment and delayed psychomotor development remained significant. These findings suggest that dexamethasone should be used with caution.

In conclusion, we found that at 18 and 24 months of age, a considerable percentage (40%) of the very prematurely born children had moderate to severely delayed mental and/or psychomotor development. Early developmental assessment seems therefore useful, since intervention programs like physical and speech therapy can then be started at an early age. In this way the development of some of these children might be improved so that they will be able to follow main stream education later in life.

Postnatal treatment with dexamethasone appeared to be one of the major risk factors for delayed (psychomotor) development.

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