Congenital diaphragmatic hernia with(out) ECMO: impaired development at 8 years

Marlous J Madderom,1 Leontien Toussaint,2 Monique H M van der Cammen-van Zijp,1,2 Saskia J Gischler,1 René M H Wijnen,1 Dick Tibboel,1 Hanneke IJsselstijn1

ABSTRACT
Objective To evaluate developmental and social-emotional outcomes at 8 years of age for children with congenital diaphragmatic hernia (CDH), treated with or without neonatal extracorporeal membrane oxygenation (ECMO) between January 1999 and December 2003.

Design Cohort study with structural prospective follow-up.

Setting Level III University Hospital.

Patients 35 children (ECMO: n=16; non-ECMO: n=19) were assessed at 8 years of age.

Interventions None.

Main outcome measures Intelligence and motor function. Concentration, behaviour, school performance, competence and health status were also analysed.

Results Mean (SD) intelligence for the ECMO group was 91.7 (19.5) versus 111.6 (20.9) for the non-ECMO group (p=0.015). Motor problems were apparent in 16% of all participants and differed significantly from the norm (p=0.015) without differences between treatment groups. For all participants, problems with concentration (68%, p<0.001) and with behavioural attention (33%, p=0.021) occurred more frequently than in reference groups, with no difference between treatment groups. School performance and competence were not affected.

Conclusions Children with CDH—whether or not treated with neonatal ECMO—are at risk for long-term morbidity especially in the areas of motor function and concentration. Despite their impairment, children with CDH have a well-developed feeling of self-competence.

INTRODUCTION
Congenital diaphragmatic hernia (CDH) is an anatomical congenital anomaly occurring in approximately 1 in 2500 births.1 Mortality and morbidity are determined by associated anomalies, the extent of lung hypoplasia and pulmonary hypertension.1 Ventilation strategies nowadays focus on minimising barotrauma1 and survival rates are approaching 80%.2 Because more children survive the neonatal period, physical and neurodevelopmental morbidities at older ages are on the rise.3

In the past decade many CDH patients, especially those with high risk CDH (respiratory insufficiency within the first 6 h of life), were treated with neonatal extracorporeal membrane oxygenation (ECMO), the use of which is decreasing nowadays.6 Some studies report an improved survival rate with the use of ECMO,7 others a relatively unchanged rate.8–10 Of all ECMO-treated neonates, CDH patients are most prone for clinical complications during ECMO treatment and long-term morbidity.11–14 ECMO treatment was found to be significantly associated with delayed neurodevelopmental outcome.3 However, this might rather be the result of severe illness necessitating ECMO than of the treatment itself.15

As all studies have different study designs it is hard to compare outcomes between CDH patients treated with or without neonatal ECMO. Also, most studies so far are limited to preschool age. We present neurodevelopmental outcomes of 8-year-old CDH children enrolled in our multidisciplinary follow-up programme. We hypothesised that they would show developmental and social-emotional impairments and that outcomes would be the worst in those treated with ECMO, who were more severely ill. Primary outcome parameters were intelligence and motor function. Secondary outcome parameters were school performance, concentration, sense of competence, health status and behaviour.

MATERIALS AND METHODS
Participants A follow-up study was conducted in 8-year-old children diagnosed with CDH and treated in their neonatal period at the Intensive Care Unit of a level III University Hospital between January 1999 and December 2003. Veno-arterial ECMO support
was given to neonates who met the entry criteria, which did not change during the study period. Artificial ventilation was administered by conventional mechanical ventilation (Babylog 8000, Drager Medical, Lubeck, Germany) or high-frequency oscillatory ventilation (Sensormedics, Bilthoven, The Netherlands).

The study was part of a structural prospective follow-up programme initiated in 1999 providing for regular assessments of lung function, exercise capacity and development until age 18 years. The Medical Ethical Review Board of Erasmus MC waived IRB approval because ‘Medical Research in Human Subjects Act does not apply to this study, since subjects are not being submitted to any handling, nor are there rules of human behaviour being imposed’. All parents provided written permission to use the data for research purposes.

**Study design**
Before assessment, parents completed questionnaires on socioeconomic status (SES) and their child’s education and health status. The children underwent a structural psychological and psychomotor assessment by a developmental psychologist and a paediatric physical therapist. Clinical and background characteristics were recorded and compared between groups (ECMO/non-ECMO) (table 1).

**Primary outcome parameters**

**Intelligence**
A short version of the Revised Amsterdam Intelligence Test was administered. Except for patients born after 2001, the short version of the Wechsler Intelligence Scale for children (WISC-III-NL) was administered to them. Both tests have good reliability and validity. IQ was classified into above average (IQ>115), average (IQ: 85–115) and below average (IQ<85).

**Motor function**
The Movement Assessment Battery for children was administered. Percentile scores were calculated for the total impairment score, which is the sum of the item scores, and for scores in three different domains (manual dexterity, ball skills and balance); a percentile score ≤P5 is indicative of a motor problem, P6 to P15 of borderline performance and >P15 of normal motor development.

**Additional psychological assessment**

**Concentration**
Concentration was measured with The Bourdon-Vos, which is a paper-and-pencil test measuring sustained selective attention and concentration in terms of speed and accuracy. It has good validity, sensitivity and reliability.

**Self-perceived competence and health status**
Self-perceived competence was measured with the Dutch adaptation of the Self Perception Profile for Children (SPPC) for 8-to-12-year-old children. The SPPC assesses a child’s sense of competence in cognitive, social and physical domains and yields a measure of general self-worth. The internal consistency and test–retest reliability of the Dutch version are acceptable. In all, 15% of the healthy reference group scores below the normal range; this percentage was set as the cut-off point.

Health status was assessed with the Pediatric Quality of Life Inventory as described previously. A scale score of 1 SD below healthy reference norm was taken to indicate impaired health status.

**Proxy-reported behaviour**
The Dutch version of the Child Behavior Checklist (CBCL)—standardised for the Dutch population from 4 to 18 years—was completed by mothers. A subclinical to clinical score in 16% of the children was used as the cut-off point for comparison with reference norms.

**Data analysis**

Normally distributed data were analysed with Student t test. The χ² test or Fisher’s exact test served to evaluate categorical data. Influences of clinical variables (ECMO treatment (yes/no); gestational age; associated anomalies; type of repair; prevalence of chronic lung disease (CLD); prolonged use of morphinometrics/sedatives (>1 month); and use of methadone (yes/no)) and background variables (gender; ethnicity and SES) on intelligence and motor function were calculated using multiple linear regression analysis. Normal probability plots were evaluated to test applicability of the model and assumptions for regression analysis. Multicollinearity was tested using the criterion that variance inflation factors should not exceed 2.5. The medical variables were individually entered into seven regression analyses to avoid the risk of multicollinearity. Data are presented as mean (SD) unless stated otherwise.

**RESULTS**

Overall, 65 CDH patients were treated between January 1999 and December 2003. A total of 35 children (ECMO n=16; non-ECMO n=19) were eligible for assessment at 8 years. Psychological and motor function assessment was completed in 52 and 51 patients, respectively (figure 1).

**Primary outcome parameters**

**Intelligence**
For four of the 52 children, no IQ was calculated (figure 1). For the remaining 28 children, the mean total IQ was 101.6 (22.3) and within the reference norm. Mean IQ significantly differed between the ECMO group (91.7 (19.5)) and non-ECMO group (111.6 (20.9)) (t=-2.599, p=0.015). The proportions of children with above average, average and below average IQ did not differ significantly between both groups (χ²=6.305, p=0.052; figure 2).

**Motor function**
Overall, 31 children underwent motor function testing (figure 1). A total of 25 children (81%; ECMO: n=10, non-ECMO: n=15) scored within normal range, one child (3%; ECMO) was classified as borderline and five children (16%; ECMO n=3, non-ECMO n=2) were classified as having a motor problem. These proportions differed significantly from the norm population (χ²=9.171, p=0.015). No significant difference in motor development was found between treatment groups (figure 3).

A percentile score within normal range was obtained in 26 children for manual dexterity (84%; ECMO n=11, non-ECMO n=15), in 20 children for ball skills (65%; ECMO n=9, non-ECMO n=11) and in 26 children for balance skills (84%; ECMO n=11, non-ECMO n=15). Ball skills differed significantly from the norm population (χ²=10.309, p=0.010). No significant differences in domain proportions were found between the treatment groups (figure 5).
Combined intelligence and motor function development

A total of 26 children (ECMO n=13; non-ECMO n=13) had both an intelligence and motor function assessment. The percentages of children with normal or impaired intelligence combined with normal or impaired motor function did not significantly differ between treatment groups ($\chi^2=7.271$, $p=0.057$) (figure 4).

Additional psychological assessment

School performance

Of all 35 children, 33 followed regular education (94%; ECMO n=15, non-ECMO n=18); 14 of these (42%; ECMO n=7, non-ECMO n=7) received extra support at school. Two children (6%, ECMO n=1, non-ECMO n=1) followed special education because of cognitive and motor function problems.
65 patients were treated for the diagnosis CDH between January 1999 and December 2003 (35 ECMO/30 non-ECMO)

24 died (18 ECMO/6 non-ECMO)

41 eligible for follow-up (63% overall survival)

6 lost to follow-up

- n=1 severely disabled (1 non-ECMO)
- n=3 canceled participation
  - n=1 mental retardation and hemiplegia (1 non-ECMO)
  - n=2 average mental and motor development at five years of age (1 non-ECMO/1 ECMO)
- n=2 excluded: older than 1 year when diagnosed (2 non-ECMO)

35 participated in the follow-up program (16 ECMO/19 non-ECMO)

Psychological assessment

32 children
(15 ECMO/17 non-ECMO)

3 children no psychological assessment

- n=1 no sufficient medication for ADHD
  (1 non-ECMO)
- n=2 special education, cognitive developmental delay
  (1 ECMO/2 non-ECMO)

Motor function assessment

31 children
(14 ECMO/17 non-ECMO)

4 children no motor function assessment

- n=1 hemiplegia
  (1 ECMO)
- n=1 psychomotor developmental delay
  (1 non-ECMO)
- n=1 low muscle tone
  (1 ECMO)
- n=1 organisational reasons
  (1 non-ECMO)

Intelligence n=28:

- n=1 organisational reasons
  (1 ECMO)
- n=3 disharmonic profile
  (3 non-ECMO; 1 average and 2 below average intelligence)

Concentration n=22:

- n=6 organisational reasons
  (3 ECMO/3 non-ECMO)
- n=4 working speed problems
  (2 ECMO/2 non-ECMO)

Feelings of competence n=28:

- n=3 organisational reasons
  (3 non-ECMO)
- n=1 difficulty understanding questions
  (1 non-ECMO)

Health status n=27:

- n=5 organisational reasons
  (5 non-ECMO)

Figure 1 Flowchart. ADHD, attentional deficit hyperactivity disorder; CDH, congenital diaphragmatic hernia; ECMO, extracorporeal membrane oxygenation; Non-ECMO, no extracorporeal membrane oxygenation; organisational reasons for no psychological assessment, the child arrived late at the follow-up appointment or was too tired to finish the entire assessment battery.

Figure 2 Intelligence in 8-year-old CDH patients. In black, below average intelligence; in white, average intelligence; in white with stripes, above average intelligence. CDH, congenital diaphragmatic hernia; ECMO, extracorporeal membrane oxygenation; Non-ECMO, no extracorporeal membrane oxygenation.
Concentration
Concentration was assessed in 22 children (figure 1). Of these, 15 (68%; ECMO n=7, non-ECMO n=8) had low to very low information-processing speed ($\chi^2=0.028, p=0.867$). Eight had low-to-very low accuracy (36%; ECMO n=5, non-ECMO n=3) ($\chi^2=1.473, p=0.387$). Information-processing speed differed significantly ($\chi^2=21.879, p<0.001$) from the reference population, but accuracy did not ($\chi^2=1.515, p=0.324$).

Self-perceived competence and health status
Four children did not complete the SPPC (figure 1). Of the 28 children tested, a below normal range score was obtained in 29% for scholastic competence (ECMO n=4, non-ECMO n=4); 11% for social acceptance (ECMO n=2, non-ECMO n=1); 18% for athletic competence (ECMO n=5, non-ECMO n=2); 21% for behavioural conduct (ECMO n=2, non-ECMO n=4); and 7% for global feeling of self-worth (ECMO n=2, non-ECMO n=0). None scored below normal for physical appearance. No significant differences were found for the entire group compared with reference norms or between the two treatment groups.

In all, 27 children filled in a Pediatric Quality of Life Inventory (figure 1). Overall, they had significantly lower health status scores than reference peers for total functioning (mean difference (MD) $-8.45, p<0.001$), physical functioning (MD $-10.71, p<0.001$), social functioning (MD $-11.14, p<0.001$), school functioning (MD $-10.22, p<0.001$) and psychosocial functioning (MD $-8.36, p<0.001$), whereas emotional functioning was not significantly different (MD $-3.70, p=0.208$). Comparison of the two treatment groups (ECMO n=12, non-ECMO n=15) revealed significantly lower scores for the ECMO group for total functioning (MD $-13.43, p=0.024$), physical functioning (MD $-14.64, p=0.044$), social functioning (MD $-16.42, p=0.012$), school functioning (MD $-15.90, p=0.027$) and psychosocial functioning (MD $-15.24, p=0.027$). Other medical variables (eg, presence of CLD) did not influence health status scores (not shown).

Figure 3  Motor function in 8-year-old CDH patients. In black, severe motor function problems; in grey, borderline motor function problems; in white, normal motor function. Number of patients is indicated in the bars. CDH, congenital diaphragmatic hernia; ECMO, extracorporeal membrane oxygenation; Non-ECMO, no extracorporeal membrane oxygenation. TIS, total impairment score.

Figure 4  Combined intelligence and motor function development. A, intelligence and motor function for extracorporeal membrane oxygenation (ECMO) group. B, intelligence and motor function for non-ECMO group; in black, both intelligence and motor function development are normal; in grey, only intelligence is impaired; in white, both intelligence and motor function development are impaired; in white with stripes, only motor function is impaired.
Proxy-reported behaviour
A total of 27 mothers filled in the CBCL and scores indicated borderline-to-clinical range for seven children (26%; ECMO n=3, non-ECMO n=4) on the total scale, for seven children (26%; ECMO n=3, non-ECMO n=4) on the internalising scale and for four children (15%; ECMO n=2, non-ECMO n=2) on the externalising scale; all proportions were not significantly different from reference population. Nine children (33%; ECMO n=4, non-ECMO n=5) were assigned borderline-to-clinical range on the attention scale; this is significantly more than in the reference population ($\chi^2=6.036, p=0.021$). No significant differences between treatment groups were found.

**Associations between outcome parameters**
ECMO treatment ($R^2=0.206, p=0.015$), having associated anomalies ($R^2=0.190, p=0.020$), CLD ($R^2=0.107, p=0.049$) and prolonged use of morphinomimetics/sedatives ($R^2=0.183, p=0.023$) negatively influenced intelligence. Having associated anomalies ($R^2=0.175, p=0.019$), CLD ($R^2=0.207, p=0.010$), and use of methadone ($R^2=0.176, p=0.021$) negatively influenced motor function. High SES ($R^2=0.285, p=0.035$) positively influenced intelligence.

Five of the six children with below average intelligence indicated on the SPFC to be satisfied with their scholastic competence. Three of these five children plus one other, with borderline or definite motor function problems, were satisfied with their athletic competence.

**DISCUSSION**
In this study we hypothesised that ECMO-treated CDH children would have poorer developmental and social-emotional outcome than those without ECMO treatment. We found intelligence in the normal range for all children together, but ECMO-treated children had significantly lower IQ. For all children together, motor function was significantly worse compared with reference peers, with no differences between treatment groups. To our knowledge, this is the first study comparing outcome in 8-year-old CDH children with and without ECMO treatment within a similar time period and in one centre.

In an earlier study we found normal intelligence for 8–12-year-old CDH children treated with neonatal ECMO before 1999. The children in the present study had normal intelligence, in line with other studies in CDH patients without ECMO treatment. Nevertheless, intelligence scores in the ECMO group were significantly lower than those in the non-ECMO group. Ultrasound examinations revealed intracranial bleeding and infarctions in only a few children in both treatment groups. These do not seem to explain the difference in IQ; perhaps we should assume that children needing ECMO were more severely ill. However, we found subtle cognitive deficits such as concentration problems in both treatment groups. Also, mothers indicated more attention problems for their children when compared with reference parents. Subtle deficits in specific areas of intelligence seem apparent in children with CDH and support the findings that CDH survivors—even those without ECMO treatment—are at risk for attention and concentration deficits. The fact that 42% of our cohort need extra support in regular education versus 21% in the Dutch reference population also points at subtle cognitive problems.

Motor problems have been reported in 60% of 1-year-old and in 75% of 5-year-old CDH children treated with and without ECMO. The present study found motor problems with ball skills particularly affected in the total CDH group, as we previously found in 5-year-old CDH children. We assume that CDH patients get little physical activity during infancy and have few opportunities to practise ball skills. Because both treatment groups showed motor problems, evaluation of motor function is important for all CDH children, irrespective of previous ECMO treatment.

When we combined intelligence and motor function outcome (n=26) we found no significant difference between the two treatment groups. However, we might have been unable to reach statistical significance due to small sample sizes. On the other hand, proportions of children with combined normal intelligence and normal motor function do seem to be higher for the non-ECMO group. This supports the idea that ECMO-treated children were more severely ill and thus experience more morbidity. We assume that for CDH patients, without severe haemorrhagic or thromboembolic complications, it need not be the ECMO treatment itself that results in worse outcome. Severity of illness, necessitating ECMO treatment, should rather be considered the main determining factor in long-term outcome.

We found a significantly lower health status for the entire cohort (with the lowest scores for ECMO-treated patients) with only emotional functioning not affected. Like emotional functioning, feelings of competence were not affected overall. It is not an unusual finding that children with objectively impaired intelligence or motor function experience normal feelings of competence.

The small sample sizes per treatment group in this study can be seen as a limitation, possibly precluding reaching statistical significance when comparing intelligence and motor functioning outcomes. Small sample sizes are not uncommon when analysing this rare diagnosis group (see online supplementary table S1). As a second limitation, data for a number of children in different neuropsychological assessments are missing (differentiated between the ECMO and non-ECMO-treated groups). The fact that children experiencing severe morbidity were the ones who were unable to complete the assessments might have resulted in a bias. This bias also shows the importance of long-term follow-up of CDH children (see online supplementary table S2 presenting long-term outcome); as more of them survive the neonatal period incidence of severe CDH-related morbidity is on the rise. This phenomenon has increasingly been identified in other studies.

**CONCLUSIONS**
Children with CDH—whether or not treated with ECMO—are at risk for long-term morbidity especially in the areas of motor function, concentration and health status. Intelligence seems within the normal range for all CDH children, with significantly lower scores for the ECMO-treated children. Despite their impairment, children with CDH have a well-developed concentration and normal motor function do seem to be higher for the non-ECMO group. The present study found motor problems with ball skills particularly affected in the total CDH group, as we previously found in 5-year-old CDH children. We assume that CDH patients get little physical activity during infancy and have few opportunities to practise ball skills. Because both treatment groups showed motor problems, evaluation of motor function is important for all CDH children, irrespective of previous ECMO treatment.

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**Contributors** MJM conceptualised and designed the study, analysed and interpreted the data, drafted the initial manuscript, and approved the final manuscript as submitted. LT and MHMvdC-vZ interpreted the data, reviewed and revised the manuscript, and approved the final manuscript as submitted. SJG and RMHW interpreted the data, critically reviewed the manuscript, and approved the final manuscript as submitted.

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manuscript as submitted. DT and HI conceptualised and designed the study, analysed and interpreted the data, reviewed and revised the manuscript, and approved the final manuscript as submitted.

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