

1 **Risk factors of impaired neuropsychological outcome in school-aged survivors of neonatal critical**  
2 **illness**

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24 neuropsychology; extracorporeal membrane oxygenation; hernias, diaphragmatic, congenital.

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1 **Abstract**

2 **Objective** Until now, long-term outcome studies have focused on general cognitive functioning and its  
3 risk factors following neonatal extracorporeal membrane oxygenation (ECMO) and/or congenital  
4 diaphragmatic hernia (CDH). However, it is currently unknown which neuropsychological domains are  
5 most affected in these patients, and which clinical variables can be used to predict specific  
6 neuropsychological problems. This study aimed to identify affected neuropsychological domains and its  
7 clinical determinants in survivors of neonatal ECMO and/or CDH.

8 **Design** Prospective follow-up study.

9 **Setting** Tertiary university hospital.

10 **Patients** Sixty-five eight-year-old survivors of neonatal ECMO and/or CDH.

11 **Interventions** None.

12 **Measurements and Main Results** Intelligence, attention, memory, executive functioning and  
13 visuospatial processing were evaluated using validated tests and compared with Dutch reference data.

14 Assessed risk factors of outcome were illness severity indicators, number of anesthetic procedures in the  
15 first year of life and growth at one year.

16 Patients had average intelligence (mean IQ $\pm$ SD:95 $\pm$ 16), but significantly poorer sustained attention (mean  
17 z-score $\pm$ SD:−2.73 $\pm$ 2.57), verbal (immediate:−1.09 $\pm$ 1.27;delayed:−1.14 $\pm$ 1.86) and visuospatial memory  
18 (immediate: −1.48 $\pm$ 1.02;delayed: −1.57 $\pm$ 1.01;recognition:−1.07 $\pm$ 3.10) than the norm. ECMO-treated  
19 CDH patients had significantly lower mean IQ (84 $\pm$ 12) than other neonatal ECMO patients (94 $\pm$ 10) and  
20 CDH patients not treated with ECMO (100 $\pm$ 20). Maximum vasoactive-inotropic score was negatively  
21 associated with delayed verbal ( $B$ =−0.02, 95%CI:−0.03 to −0.002,  $p$ =.026) and visuospatial memory  
22 ( $B$ =−0.01, 95%CI:−0.02 to −0.001,  $p$ =.024).

23 **Conclusions** We found memory and attention deficits in eight-year-old neonatal ECMO and CDH  
24 survivors. The maximum dose of vasoactive medication was negatively associated with verbal and  
25 visuospatial memory, which may suggest an effect of early cerebral hypoperfusion in determining these  
26 abnormalities.

1 **Introduction**

2 The majority of children growing up following neonatal extracorporeal membrane oxygenation (ECMO)  
3 and/or congenital diaphragmatic hernia (CDH) have a generally average IQ, yet show impaired  
4 neurodevelopmental outcome and school problems.(1-3) Until now, most long-term studies of school-age  
5 survivors have focused on IQ and attention, hampering our understanding of the specific  
6 neuropsychological problems after neonatal critical illness.(1-3) Furthermore, it remains largely unclear  
7 which patients are at risk of impaired outcome and why. For early identification and intervention of  
8 patients at risk, it is crucial to increase our understanding of neuropsychological domains most frequently  
9 impaired and the risk factors determining impaired outcome.

10 Earlier studies have found that markers of illness severity, such as ECMO requirement and the  
11 presence of chronic lung disease, were predictive of neuropsychological deficits in CDH patients.(2) Still,  
12 clinically useful risk factors of such deficits following neonatal critical illness remain unknown. Our  
13 group has recently shown specific hippocampal volume alterations that were related to verbal memory  
14 impairments in school-aged neonatal ECMO survivors.(4,5) The hippocampus appears specifically  
15 vulnerable to hypoxic-ischemic injuries.(6,7) Using measures of hypoperfusion could possibly aid in  
16 predicting neuropsychological outcomes following neonatal critical illness, as hypoperfusion may result  
17 in hypoxic-ischemic and eventually reperfusion injury in the hippocampus. Additionally, poor growth in  
18 the first year of life has been reported in CDH and ECMO-treated patients(8,9) and has been associated  
19 with worse neurodevelopmental outcome.(10,11) However, the effects of poor growth on specific  
20 neuropsychological functions in school-aged survivors of neonatal critical illness remain unknown.

21 In this study, neuropsychological outcome was evaluated in school-aged CDH survivors treated  
22 with or without neonatal ECMO and in neonatal ECMO-treated survivors following other diagnoses. We  
23 hypothesized that children would mainly have attention and memory deficits, despite a generally average  
24 IQ. We expected markers of increased severity of illness and hypoperfusion as well as poor growth in the  
25 first year of life to have negatively affected neuropsychological outcome at school-age.

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1 **Material and Methods**

2 *Population*

3 We included CDH and neonatal ECMO patients born between January 2006 and March 2009.  
4 Participants were routinely seen at eight years as part of a structured prospective longitudinal follow-up  
5 program that includes regular physical and neurodevelopmental assessments until 18 years.(12) ECMO  
6 treatment was applied in case of severe respiratory failure using the criteria described by Stolar et al.(13).  
7 Since November 2007, CDH patients were treated according to the standardized CDH-EURO Consortium  
8 treatment protocol.(14) In case of persistent poor tissue perfusion and/or hypotension (arterial blood  
9 pressure below normal levels for gestational age and not improving after fluid boluses), treatment with  
10 dobutamine and/or dopamine was initiated, followed by norepinephrine, epinephrine or milrinone in case  
11 of persistent hypotension. Exclusion criteria were: genetic syndromes known to affect neurodevelopment,  
12 severe neurologic or developmental impairments preventing standardized assessments, late CDH  
13 diagnosis(>7 days of life), or a paraesophageal hernia. We used a protocol with extended  
14 neuropsychological assessments, implemented in January 2014 (Supplemental File 1).(1,2) Included  
15 children were divided into three groups: ECMO patients following other diagnoses than CDH(“ECMO-  
16 other”), CDH patients treated with ECMO(“CDH-ECMO”) and CDH patients not treated with  
17 ECMO(“CDH-non-ECMO”). This post-ECMO/CDH follow-up program is standard of care, therefore  
18 Institutional Review Board approval was waived(MEC-2017-185).(2,15)

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20 *Data collection*

21 Relevant clinical data were collected at the time of hospitalization (Supplemental Methods). The Pediatric  
22 Logistic Organ Dysfunction-2(PELOD-2) score(16) was collected in the first 24 hours of pediatric  
23 intensive care unit(PICU) stay (or up to ECMO cannulation in ECMO-treated patients if ECMO was  
24 initiated within the first 24 hours of PICU stay), the maximum vasoactive-inotropic score(VIS)(17) was  
25 recorded up until ECMO cannulation for the ECMO-treated patients or up until hernia repair for the  
26 CDH-non-ECMO patients.

1 Follow-up data included growth measurements (height, weight, head circumference) at 6 months  
2 and 1 year, which were converted into z-scores (individual score minus the norm score divided by the  
3 norm SD).(19) Height-corrected-for-target height z-score was calculated as follows: height-for-age z-  
4 score–target height z-score.(20)

5 Neuropsychological evaluation was performed by an experienced pediatric psychologist.  
6 Socioeconomic status was assessed from maternal education level.(21)

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### 8 *Neurodevelopmental outcome tests*

9 Validated neuropsychological tests were administered in their Dutch versions to assess skills in six  
10 domains (Supplemental File 1):

11 1 *IQ*: Two-subtest short-form(Block Design and Vocabulary) of the Wechsler Intelligence  
12 Scale for Children(WISC-III-NL)(22).

13 2 *Attention*:

14 a. *Processing speed*: Trail Making Test section A(TMTA)(23,24).

15 b. *Selective attention and cognitive flexibility*: STROOP color-word test(stroop)(23,24) and  
16 Trail Making Test section B(TMTB)(23,24).

17 c. *Sustained attention*: Dot Cancellation Test(DCT)(25).

18 3 *Verbal memory*:

19 a. *Working-memory*: subtest Digit Span of the WISC-III-NL(22).

20 b. *Immediate and delayed recall*: Rey Auditory Verbal Learning Test(RAVLT)(26).

21 4 *Visuospatial memory*:

22 a. *Working-memory*: subtest Spatial Span of the Wechsler Nonverbal Scale of  
23 Ability(WNV)(27).

24 b. *Immediate and delayed recall*: Rey Complex Figure Test(RCFT)(28).

25 5 *Executive functioning*: Key Search and Modified Six Elements of the Behavioral Assessment  
26 of the Dysexecutive Syndrome(BADS-C-NL)(29).

1           6           *Visuospatial processing: Copy of the Rey Complex Figure Test(RCFT Copy)(28).*

2 Neuropsychological test scores were converted into z-scores. Scores were inverted where appropriate so  
3 that a higher score always equated with better performance. Z-scores  $\leq -1$  were regarded as likely to  
4 represent impaired functioning (general population:mean z-score=0; SD=1)(23).

5  
6 *Statistical analysis*

7 Differences in patient characteristics between the three groups(ECMO-other, CDH-ECMO and CDH-  
8 non-ECMO) were evaluated with chi-square or Fisher's exact tests for categorical variables, and with  
9 independent samples t-tests and one-way analysis of variance(ANOVA) for normally distributed  
10 variables. Mann-Whitney U tests and Kruskal-Wallis tests were used for continuous variables that were  
11 not normally distributed. Differences in neuropsychological outcome between the three groups were  
12 assessed with one-way ANOVA.

13           Univariable analyses were performed to assess the influence of clinical characteristics on the  
14 following neuropsychological outcomes of interest: intelligence, sustained attention, verbal memory  
15 immediate recall, verbal memory delayed recall, visuospatial memory immediate recall and visuospatial  
16 memory delayed recall. The independent variables included: maximum VIS, ECMO, type of  
17 ECMO(venoarterial or venovenous), sepsis, ventilator-free days in the first 28 days of life, duration of  
18 initial hospital stay, growth z-scores at 1 year (paired t-test showed largest growth deflection from 6  
19 months to 1 year) and number of anesthetic procedures during the first year of life.Next, multivariable  
20 linear regression analyses were used to identify which independent variables remained significant  
21 predictors in a multivariable model. The assumptions for linear regression analysis were checked with  
22 normal probability plots of the residuals. Multicollinearity was evaluated in the multivariable models  
23 using the criterion that variance inflation factors should not exceed 2.5(30).

24           Analyses were performed with SPSS 21.0(IBM, Armonk, NY, USA), a two-sided *p*-value<.05 was  
25 considered statistically significant.

1 **Results**

2 *Patient characteristics*

3 Sixty-five patients aged  $8.0 \pm 0.6$  years were included: 25 ECMO-other patients, 10 CDH-ECMO patients,  
4 and 30 CDH-non-ECMO patients(Supplemental Figure 1). Illness severity during hospital admission  
5 differed between the three groups(Table 1). The CDH-ECMO patients had the highest PELOD-2 score,  
6 the highest maximum VIS, the highest rate of sepsis, and the longest duration of mechanical ventilation  
7 and hospital stay. Sepsis occurred in three ECMO-other patients (during ECMO:n=2; after ECMO:n=1),  
8 four CDH-ECMO patients (after ECMO:n=4), and one CDH-non-ECMO patient after hernia repair. Four  
9 (50%) patients required vasoactive medication during sepsis. The median maximum VIS during sepsis  
10 was lower than the median maximum VIS before the ECMO run and none of the patients had a higher  
11 maximum VIS during sepsis(Table 1). Characteristics of eligible patients who were lost to follow-up or  
12 refused follow-up (n=14) did not differ from included patients(data not shown). None of the patients  
13 treated with ECMO (both ECMO-other and CDH-ECMO) had signs of cerebral hemorrhage or vessel  
14 occlusion on cranial ultrasounds performed before and after the ECMO run.

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16 *Neuropsychological outcome*

17 IQ fell within the normal range for the group as a whole. Sustained attention, verbal memory (immediate  
18 and delayed recall) and visuospatial memory (immediate and delayed recall as well as recognition) were  
19 below average compared to the general population(Table 2). The majority of patients had normal  
20 outcomes in working-memory, executive functioning and visuospatial processing. However, over 50%  
21 had impaired outcomes ( $z\text{-score} \leq -1$ ) on one or more of the memory and attention tests(Figure 1).

22 When analyzing the three groups separately, we found that CDH survivors treated with ECMO  
23 had a significantly lower IQ compared to both other groups. However, no significant differences were  
24 found between the three groups on any of the other neuropsychological outcomes(Table 2).

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1 *Predictors of neuropsychological outcome*

2 Table 3 shows the results of the regression analyses. In the univariable analyses, severity of illness  
3 indicated by the need for ECMO, treatment with venoarterial-ECMO, maximum VIS, ventilator-free  
4 days, and duration of initial hospital stay were associated with neuropsychological outcome, in particular  
5 with IQ. The number of anesthetic procedures during the first year of life was associated with IQ and  
6 sustained attention, and weight-for-height at 1 year was positively associated with IQ.

7         In the multivariable analyses, a higher maximum VIS remained associated with worse verbal and  
8 visuospatial memory delayed recall, such that an increase in maximum VIS of 20 points would result in a  
9 decrease of the verbal and visuospatial memory delayed recall z-scores of 0.4 and 0.2, respectively.  
10 Patients with impaired verbal memory had a significantly higher maximum VIS(72±44) than patients with  
11 normal verbal memory (40±32), $p=.003$ . Patients with impaired visuospatial memory had a higher  
12 maximum VIS (64±45) than patients with normal visuospatial memory(44±33), although this was not  
13 significant( $p=.118$ ). The VIS remained a significant predictor of verbal and visuospatial memory delayed  
14 recall when group (ECMO-other, CDH-ECMO, CDH-non-ECMO) was added to the model (data not  
15 shown).

16         Growth or other illness severity indicators were no longer associated with neuropsychological  
17 outcome in the multivariable analyses(Supplemental Table 1).

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1 **Discussion**

2 This is the first study evaluating all major neuropsychological domains in school-aged survivors of  
3 neonatal ECMO and/or CDH. We found sustained attention and verbal and visuospatial memory deficits  
4 in over half of the patients, while other neuropsychological domains fell within the average range. CDH  
5 survivors treated with ECMO had lower IQ than the other two groups, who had an average IQ.  
6 Nonetheless, the observed attention and memory problems were more severe than expected based on their  
7 IQ. This incongruity between attention and memory problems with IQ for all three groups indicates  
8 specific impairments in these domains. A higher dose of vasoactive medication (indicated by the  
9 maximum VIS recorded up until ECMO cannulation or hernia repair) was associated with lower scores on  
10 verbal and visuospatial memory delayed recall. Interestingly, impaired memory and attention were found  
11 in all diagnostic groups, except for better, although not significantly, verbal memory in the CDH-non-  
12 ECMO group (within one standard deviation of the norm). Attention deficits have been reported in these  
13 patients previously, also despite generally average IQ.(1-3,15) However, other neuropsychological  
14 domains were not assessed in these studies. In the present study, we evaluated all major  
15 neuropsychological domains, and thereby identified a specific neuropsychological profile following  
16 ECMO and/or CDH. Our findings may serve as a starting point for intervention-based studies designed to  
17 improve cognitive functioning in these children.

18 As we found memory and attention deficits in the majority of patients, it is imperative to identify  
19 potential risk factors. Over the years, several severity of illness scoring systems have been developed  
20 including the VIS.(17) In the univariable analyses, maximum VIS as well as ventilator-free days and  
21 duration of initial hospital stay were independently associated with neuropsychological outcome, mainly  
22 with IQ. This indicates that severity of illness plays an important role in determining cognitive outcome in  
23 these survivors. Interestingly, in the multivariable analyses, only the maximum VIS recorded up until  
24 ECMO cannulation or hernia repair remained associated with delayed verbal and visuospatial memory.  
25 The hippocampus is highly involved in delayed memory and has previously been shown to be altered  
26 following ECMO and/or CDH.(4,5,31,32) The hippocampus has been found to be particularly susceptible

1 to cerebral hypoperfusion resulting in hypoxia-ischemia.(6,7,33) Although this study does not show a  
2 causative effect of vasoactive medication regarding memory problems, we speculate that receiving high  
3 levels of vasoactive medication in the first period of life may be an indirect marker of temporarily  
4 (regional) inadequate brain perfusion. A high need for vasoactive medication could therefore be a useful  
5 component in estimating severity of illness and risk of memory impairments at school-age in these  
6 survivors. Although we cannot make any recommendations based on our findings, the VIS may be  
7 valuable in determining the need for and timing of ECMO treatment in neonates with severe respiratory  
8 failure, which should be investigated in future studies. As the VIS has been validated to predict clinical  
9 outcomes in infants who require cardiac surgery(17,34), representing another group of critically ill  
10 children requiring circulatory support by vasopressor drugs. Future studies are needed to further validate  
11 the usefulness of this score for long-term outcome in neonatal critical illness survivors, and to study the  
12 direct association between maximum VIS and brain areas susceptible to ischemic-reperfusion injury such  
13 as the hippocampus.

14         Attention and memory problems at school-age have also been found in other groups of critically  
15 ill neonates such as premature infants and infants with congenital heart disease.(31, 35) Studies in  
16 premature infants have found that lower scores on executive functioning were associated with the severity  
17 of illness(36), although others have not confirmed this(37). Multicenter studies are needed to develop a  
18 multimodal prediction model which may be the key to earlier identification of critical illness survivors at  
19 risk of impaired neurodevelopmental outcome. Predictors of interest would be specific markers of illness  
20 severity, such as the maximum VIS, in combination with predetermined assessment of neurobiological  
21 correlates, such as imaging of the hippocampus.

22         We did not find any associations between growth at one year and long-term neuropsychological  
23 outcome. Although many CDH patients show poor growth during the first year of life(9), only one study  
24 has found an association between weight and head circumference at 2-3 years and general cognitive  
25 functioning, although not at five years.(11) In premature infants, several studies have demonstrated a  
26 positive association between weight gain and head growth and cognitive outcomes.(10) However, a recent

1 study in children with extremely low birth weight showed no effect of catch-up-growth in the first two  
2 years of life on neurocognitive outcome at 11 years.(38) Most studies in premature infants did not take  
3 into account the difference in severity of illness. It is therefore uncertain whether poor growth itself or  
4 severity of critical illness leading to poor growth, is more important in determining adverse  
5 neuropsychological outcome in premature infants. Although we cannot draw definitive conclusions, our  
6 study indicates that in ECMO and CDH patients, the severity of illness has a greater impact on  
7 neuropsychological outcome than growth in the first year of life.

8 Our study has some limitations. First, the relatively small sample sizes of the three diagnostic  
9 groups is a frequent problem in follow-up studies including patients with rare diagnoses limiting the  
10 interpretability of our regression analyses. Multicenter collaborations with standardized management and  
11 structured follow-up are important to increase sample sizes and get a better understanding of the  
12 pathophysiology underlying long-term outcome. Second, MRI data were not available and we therefore  
13 could not examine whether maximum VIS was associated with brain structures susceptible to cerebral  
14 hypoperfusion. Standardized neuroimaging studies both at neonatal and school-age will aid in  
15 understanding pathophysiologic concepts of early brain development and long-term outcome, and are  
16 therefore important in future studies. Third, there are likely multiple factors involved in the development  
17 of long-term neuropsychological impairments following ECMO and/or CDH, such as exposure to  
18 inflammation(7), anesthetics(39), and stress(40) in early life, and/or a complex interplay amongst these  
19 factors. As of now, techniques to reliably measure these mechanisms and their interactions are lacking.  
20 Future studies are needed to develop specific brain monitoring techniques that can be used during PICU  
21 stay for early identification of patients at risk of long-term impairments.

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1 **Conclusions**

2 We found sustained attention, verbal and visuospatial memory deficits in eight-year-old survivors of  
3 neonatal ECMO and/or CDH. These findings emphasize the need for standardized neuropsychological  
4 follow-up including attention and memory assessments until school-age and beyond in these survivors.  
5 Maximum VIS in the first day(s) of PICU admission was negatively associated with verbal and  
6 visuospatial memory at eight years. This suggests that this measure of severity of illness, possibly  
7 indicating (cerebral) hypoperfusion during early life, is related to specific neuropsychological functions in  
8 eight year-old neonatal ECMO and/or CDH survivors. Future studies using advanced neuroimaging  
9 techniques in combination with clinical characteristics and neuropsychological evaluation will aid in a  
10 better understanding of this finding and are needed for early identification and intervention of patients at  
11 risk. Our findings of specific attention and memory problems can serve as a starting point for developing  
12 and implementing early intervention strategies that focus on improving attention and memory in these  
13 patients.

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1 **Tables**

<b>Table 1. Patient characteristics</b>				
Characteristics	ECMO-other <sup>1</sup> (n = 25)	CDH-ECMO (n = 10)	CDH-non-ECMO (n = 30)	p-value
Gestational age (weeks)	40.9 (40.0-41.1)	39.2 (36.7-40.7)	38.5 (38.0-39.3)	<b>&lt;0.001</b>
Birth weight (kilograms)	3.5 (0.5)	3.1 (0.8)	2.9 (0.4)	<b>0.001</b>
Male	14 (56%)	5 (50%)	18 (60%)	0.84 <sup>†</sup>
Ethnicity				0.60 <sup>†</sup>
Dutch	19 (76%)	9 (90%)	26 (87%)	
Other	6 (24%)	1 (10%)	4 (13%)	
Maternal Education Level				0.59 <sup>2</sup>
Low	6 (24%)	3 (33%)	8 (29%)	
Moderate	12 (48%)	3 (33%)	16 (57%)	
High	7 (28%)	3 (33%)	4 (14%)	
Unknown	0	1	2	
Inborn	4 (16%)	4 (40%)	18 (60%)	<b>0.003<sup>2</sup></b>
<b><i>ECMO-related</i></b>				
Highest oxygenation index prior to ECMO	33 (28-40)	38 (26-54)		0.72
Age start ECMO (days)	2 (1-4)	1 (1-2)		0.30
Duration of ECMO (hours)	92 (54-100)	172 (131-212)		<b>&lt;0.001</b>
ECMO mode				<b>&lt;0.001<sup>2</sup></b>
VA	7 (28%)	10 (100%)		
VV converted to VA	1 (4%)			
VV	17 (68%)			
<b><i>CDH-related</i></b>				
Left sided hernia		8 (80%)	25 (83%)	1.00 <sup>2</sup>
Age at surgery (days)		4 (3-6)	3 (2-4)	0.32
Patch repair		9 (90%)	17 (57%)	0.07 <sup>2</sup>
Surgical technique				
Laparotomy		10 (100%)	20 (67%)	<b>0.04<sup>2</sup></b>
Thoracoscopy			10 (33%)	
<b><i>Hospital Admission-related</i></b>				
PELOD-2 score <sup>3</sup>	7 (7-9)	9 (8-9)	6 (5-7)	<b>&lt;0.001</b>
Maximum VIS <sup>4</sup>	40 (35-70)	107 (91-142)	40 (5-76)	<b>&lt;0.001</b>
Dobutamine treatment	24 (96%)	10 (100%)	19 (63%)	<b>0.04<sup>2</sup></b>
Dopamine treatment	22 (88%)	7 (70%)	13 (43%)	<b>0.01<sup>2</sup></b>
Norepinephrine treatment	13 (52%)	10 (100%)	15 (50%)	<b>0.02<sup>2</sup></b>
Epinephrine treatment	2 (8%)	-	2 (7%)	1.00 <sup>2</sup>
Milrinone treatment	-	2 (20%)	-	<b>0.03<sup>2</sup></b>
Vasopressin treatment	-	-	-	-
CPR during initial hospital stay	2 (8%)	1 (10%)	0 (0%)	0.18 <sup>2</sup>
Sepsis during initial hospital stay <sup>5</sup>	3 (12%)	4 (40%)	1 (3%)	<b>0.01<sup>2</sup></b>
Days of mechanical ventilation	10 (7-11)	40 (16-51)	10 (5-18)	<b>0.001</b>

Ventilator-free days in the first 28 days of life	18 (17-21)	0 (0-12)	19 (10-23)	<b>0.001</b>
Days of initial PICU stay	13 (10-16)	70 (24-101)	21 (12-35)	<b>&lt;0.001</b>
Days of initial hospital stay	24 (21-29)	91 (48-156)	36 (20-53)	<b>0.004</b>
Pulmonary hypertension				
Yes	13 (57%)	8 (80%)	12 (48%)	0.25 <sup>2</sup>
No	10 (43%)	2 (20%)	13 (52%)	
Missing	2	0	5	
Inhaled nitric oxide treatment	22 (88%)	10 (100%)	10 (33%)	<b>&lt;0.001<sup>2</sup></b>
Sildenafil treatment	2 (8%)	6 (60%)	1 (3%)	<b>&lt;0.001<sup>2</sup></b>
Chronic lung disease <sup>6</sup>				
Yes	2 (10%)	8 (80%)	8 (28%)	<b>&lt;0.001<sup>2</sup></b>
No	19 (90%)	2 (20%)	21 (72%)	
Missing	4		1	
<b><i>Follow-up</i></b>				
Number of anesthetic procedures first year of life	2 (2-3)	4 (3-4)	1 (1-2)	<b>&lt;0.001</b>
Weight-for-height z-score at 1 year	-0.38 (0.86)	-1.80 (0.76)	-0.88 (0.97)	<b>0.001</b>
Height-corrected-for-target height z-score at 1 year	-0.27 (0.96)	-0.36 (0.69)	-0.43 (0.78)	<b>0.02</b>
Head circumference-for-age z-score at 1 year	-0.47 (1.16)	-0.50 (1.31)	-0.39 (1.15)	0.96

Data are expressed as mean (standard deviation), median (interquartile range) or number (percentage), as appropriate.

**P-value** = significant difference between the groups.

<sup>1</sup> ECMO treatment was given in case of meconium aspiration syndrome (n = 18), persistent pulmonary hypertension of the newborn (n = 2), congenital heart disease (monocentric heart with transposition of the great vessels and total anomalous pulmonary venous return) (n = 1), sepsis (n = 1), respiratory insufficiency due to respiratory syncytial virus (n = 1), infant respiratory distress syndrome with bilateral pneumothorax (n = 1), pulmonary hypoplasia due to bilateral hydrothorax (n = 1).

<sup>2</sup> Fisher's exact test was used.

<sup>3</sup> PELOD-2 score in the first 24 hours of PICU stay or up to ECMO cannulation if ECMO was initiated in the first 24 hours of PICU stay was calculated.<sup>16</sup>

<sup>4</sup>The maximum VIS recorded during PICU stay up until ECMO cannulation for the ECMO-treated patients or up until hernia repair for the CDH non-ECMO patients.<sup>17</sup> VIS was maximal at the median age of 1 (1-1) day in the ECMO patients, at the median age of 1 (0-1) day in the CDH ECMO patients, and at the median age of 0 (0-1) days in the CDH non-ECMO patients.

<sup>5</sup> Sepsis during initial hospital stay (clinical suspicion of sepsis with positive blood culture). ECMO-other: 2 patients had sepsis during ECMO; 1 patients after ECMO; maximum VIS during sepsis: 10 (5-15). CDH-ECMO: 4 patients had sepsis after ECMO; maximum VIS during sepsis: 2.5 (0-32.5). CDH non-ECMO: 1 patient had sepsis after hernia repair; maximum VIS during sepsis: 0.

<sup>6</sup> Chronic lung disease defined as oxygen dependency at 28 days of life.<sup>18</sup>

Abbreviations: CDH = congenital diaphragmatic hernia; CPR = cardiopulmonary resuscitation; ECMO = extracorporeal membrane oxygenation; PELOD-2 = Pediatric Logistic Organ Dysfunction-2; PICU=pediatric intensive care unit; VA = veno-arterial; VIS = vasoactive-inotropic score; VV = veno-venous.

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**Table 2. Overview of neuropsychological assessment outcome**

Neuropsychological test	All (n = 65)	ECMO-other (n = 25) <sup>1</sup>	CDH-ECMO (n = 10)	CDH-non-ECMO (n = 30)	<i>p</i> -value
<i>Intelligence</i>					
WISC-III-NL	95 (16)	94 (10)	84 (12)	100 (20)	<b>.029</b>
<i>Attention</i>					
TMT A	-0.33 (0.86)	-0.25 (1.05)	-0.45 (0.53)	-0.36 (0.79)	.963
TMT B	-0.18 (0.98)	0.08 (1.03)	-0.28 (1.08)	-0.37 (0.88)	.267
STROOP	-0.61 (1.01)	-1.00 (0.76)	-0.29 (1.11)	-0.39 (1.10)	.081
DCT	-2.73 (2.57)	-2.88 (2.09)	-3.88 (2.91)	-2.25 (2.76)	.173
<i>Verbal memory</i>					
WISC-III-NL Digit span	0.06 (1.09)	-0.08 (1.15)	-0.34 (0.94)	0.31 (1.07)	.706
RAVLT immediate	-1.09 (1.27)	-1.26 (1.24)	-1.55 (1.03)	-0.79 (1.33)	.664
RAVLT delayed	-1.14 (1.86)	-1.38 (1.46)	-1.87 (1.16)	-0.70 (2.24)	.117
<i>Visuospatial memory</i>					
WNV Spatial Span	-0.31 (0.99)	-0.39 (0.79)	-0.85 (0.76)	-0.06 (1.14)	.613
RCFT immediate	-1.48 (1.02)	-1.52 (1.02)	-1.86 (0.69)	-1.31 (1.09)	.417
RCFT delayed	-1.57 (1.01)	-1.56 (1.01)	-1.89 (0.77)	-1.47 (1.09)	.689
RCFT recognition	-1.07 (3.10)	-1.09 (1.51)	-0.62 (0.95)	-0.47 (1.22)	.117
<i>Executive functioning</i>					
Key Search	-0.12 (0.94)	-0.26 (0.98)	-0.04 (1.09)	-0.05 (0.89)	.694
Modified Six Elements	-0.60 (0.87)	-0.95 (0.90)	-0.46 (0.47)	-0.46 (0.92)	.194
<i>Visual spatial processing</i>					
RCFT copy	-0.26 (1.02)	-0.36 (1.00)	-0.69 (1.02)	-0.02 (1.01)	.107

Mean (standard deviation)=average IQ score or average z-score of the neuropsychological test.

One-way analysis of variance was used to identify differences between the groups on neuropsychological outcome.

**P-value**=significant difference between the groups.

<sup>1</sup> ECMO treatment was given in case of meconium aspiration syndrome (n = 18), persistent pulmonary hypertension of the newborn (n = 2), congenital heart disease (monovalentricular heart with transposition of the great vessels and total anomalous pulmonary venous return) (n = 1), sepsis (n = 1), respiratory insufficiency due to respiratory syncytial virus (n = 1), infant respiratory distress syndrome with bilateral pneumothorax (n = 1), pulmonary hypoplasia due to bilateral hydrothorax (n = 1).

Abbreviations: CDH = congenital diaphragmatic hernia; DCT = dot cancellation test; ECMO = extracorporeal membrane oxygenation; RAVLT = Rey auditory verbal learning test; RCFT = Rey complex figure test; STROOP = Stroop color word test; TMT = trail making test; WISC-III-NL = Wechsler Intelligence Scale for Children, Dutch version.

Please refer to supplementary file 1 for a description of the neuropsychological tests.

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**Table 3. Patient characteristics and neuropsychological outcome at eight years of age**

Variables	Intelligence	Sustained attention	Verbal memory immediate	Verbal memory delayed	Visuospatial memory
<i>Univariable analyses with medical predictors</i>					
CDH-non-ECMO <sup>1</sup>	<b>B = 9.84, p = .031</b> (CI 0.96 – 18.72)	<b>B = 1.73, p = .016</b> (CI 0.34 – 3.12)	B = 0.70, p = .068 (CI -0.05 – 1.46)	B = 0.86, p = .145 (CI -0.31 – 2.02)	B = 0.31, p = .481 (CI -0.22 – 0.84)
CDH-ECMO <sup>2</sup>	<b>B = -14.11, p = .016</b> (CI -25.48 – -2.74)	B = -1.84, p = .060 (CI -0.08 – 3.76)	B = -0.73, p = .144 (CI -1.73 – 0.26)	B = -0.97, p = .204 (CI -2.48 – 0.54)	B = -0.01, p = .978 (CI -0.91 – 0.89)
ECMO-other <sup>3</sup>	B = -1.59, p = .745 (CI -11.37 – 8.19)	B = -0.77, p = .312 (CI -2.30 – 0.75)	B = -0.29, p = .475 (CI -1.11 – 0.53)	B = -0.31, p = .622 (CI -1.55 – 0.94)	B = -0.41, p = .501 (CI -1.65 – 0.83)
VA-ECMO <sup>4</sup>	<b>B = -12.59, p = .002</b> (CI -19.97 – -5.20)	B = -0.42, p = .670 (CI -2.46 – 1.61)	B = -0.38, p = .457 (CI -1.41 – 0.66)	B = -0.25, p = .677 (CI -1.47 – 0.97)	B = -0.21, p = .731 (CI -1.45 – 0.99)
Sepsis <sup>5</sup>	B = -12.36, p = .064 (CI -25.46 – 0.74)	B = -0.86, p = .451 (CI -1.42 – 3.15)	B = -0.52, p = .363 (CI -1.65 – 0.62)	B = -0.93, p = .281 (CI -2.63 – 0.78)	B = -0.21, p = .731 (CI -1.45 – 0.99)
VIS <sup>6</sup>	B = -0.08, p = .105 (CI -0.17 – 0.02)	B = -0.01, p = .217 (CI 0.01 – -0.03)	<b>B = -0.01, p = .014</b> (CI -0.02 – -0.002)	<b>B = -0.02, p = .004</b> (CI -0.03 – -0.01)	<b>B = -0.01, p = .004</b> (CI -0.02 – -0.002)
Ventilator-free days <sup>7</sup>	<b>B = 0.70, p = .006</b> (CI 0.22 – 1.19)	B = 0.07, p = .098 (CI 0.16 – -0.01)	<b>B = 0.04, p = .035</b> (CI 0.00 – 0.09)	<b>B = 0.08, p = .025</b> (CI 0.01 – 0.14)	<b>B = 0.01, p = .004</b> (CI 0.00 – 0.02)
Initial hospital stay (days)	<b>B = -0.16, p = .004</b> (CI -0.27 – -0.06)	B = -0.01, p = .133 (CI 0.00 – -0.03)	<b>B = -0.01, p = .045</b> (CI -0.02 – 0.000)	B = -0.01, p = .133 (CI -0.03 – 0.004)	B = -0.01, p = .133 (CI -0.03 – 0.004)
Anesthetics <sup>8</sup>	<b>B = -2.92, p = .027</b> (CI -5.49 – -0.35)	<b>B = -0.44, p = .036</b> (CI -0.03 – -0.85)	B = -0.15, p = .179 (CI -0.37 – 0.72)	B = -0.23, p = .175 (CI -0.57 – 0.11)	B = -0.01, p = .978 (CI -0.91 – 0.89)
<i>Univariable analyses with growth predictors</i>					
Weight-for-height z-score at 1 year	<b>B = 6.41, p = .002</b> (CI 2.48 – 10.33)	B = 0.42, p = .275 (CI -0.35 – 1.19)	B = 0.35, p = .053 (CI -0.01 – 0.69)	B = 0.29, p = .323 (CI -0.30 – 0.89)	B = 0.21, p = .237 (CI -0.14 – 0.55)
Height-corrected-for-target height z-score at 1 year	B = 0.54, p = .835 (CI -4.70 – 5.79)	B = 0.21, p = .639 (CI 0.68 – 1.10)	B = 0.28, p = .203 (CI -0.16 – 0.71)	B = 0.38, p = .287 (CI -0.33 – 1.09)	B = -0.01, p = .978 (CI -0.91 – 0.89)
Head circumference-for-age z-score at 1 year	B = 3.98, p = .060 (CI -0.18 – 8.13)	B = 0.27, p = .413 (CI -0.39 – 0.94)	B = 0.21, p = .237 (CI -0.14 – 0.55)	B = 0.23, p = .445 (CI -0.37 – 0.83)	B = 0.11, p = .181 (CI -0.36 – 0.58)
<i>Multivariable analyses</i>					
VIS					<b>B = -0.02, p = .026</b> (CI -0.03 – -0.002)

Maternal education level, ethnicity and gender were adjusted for in all models. Growth parameters were z-scores. Variable predictors in the univariable analyses were added into the multivariable model. Only those variables found to be significant are reported. Results indicate significant associations at *p-value* < .05.

<sup>1</sup> CDH -non-ECMO patients were compared to patients treated with ECMO.

<sup>2</sup> CDH-ECMO patients were compared to patients treated with ECMO following other diagnoses and to CDH patients not treated with ECMO.

<sup>3</sup> ECMO patients following other diagnosis were compared to CDH patients treated with and without ECMO.

<sup>4</sup> Patients treated with VA-ECMO were compared to patients treated with VV-ECMO.

<sup>5</sup> Sepsis during initial hospital stay (clinical suspicion of sepsis with positive blood culture).

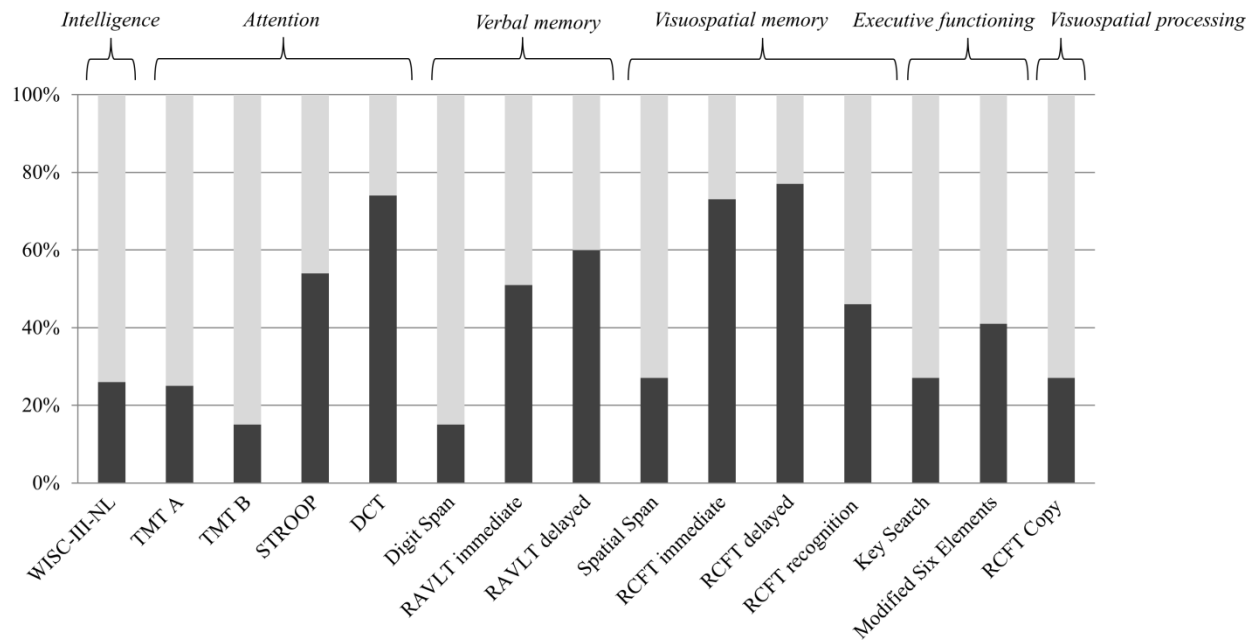
<sup>6</sup> The maximum VIS recorded during pediatric intensive care unit stay up until ECMO cannulation for the ECMO-treated patients and the CDH-non-ECMO patients.

<sup>7</sup> Ventilator-free days in the first 28 days of life.

<sup>8</sup> Number of anesthetic procedures in the first year of life.

Abbreviations: CDH = congenital diaphragmatic hernia; ECMO = extracorporeal membrane oxygenation; VIS = vasoactive drug index; CI = confidence interval; VA-ECMO = venoarterial extracorporeal membrane oxygenation; VV-ECMO = venovenous extracorporeal membrane oxygenation.

1 **Figures**



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3 **Figure 1 Presence of neuropsychological impairments in the study population**

4 Percentage of patients with a z-score  $\leq -1$  (impaired; as shown by the dark colored bars) and  $> -1$  (normal;  
5 as shown by the grey colored bars) on each of the neuropsychological tests.

6 Abbreviations: WISC-III-NL = Wechsler Intelligence Scale for Children, Dutch version; TMT = Trail

7 Making Test; Stroop = Stroop Color Word Test; DCT = Dot Cancellation Test; RAVLT = Rey Auditory

8 Verbal Learning Test; RCFT = Rey Complex Figure Test.

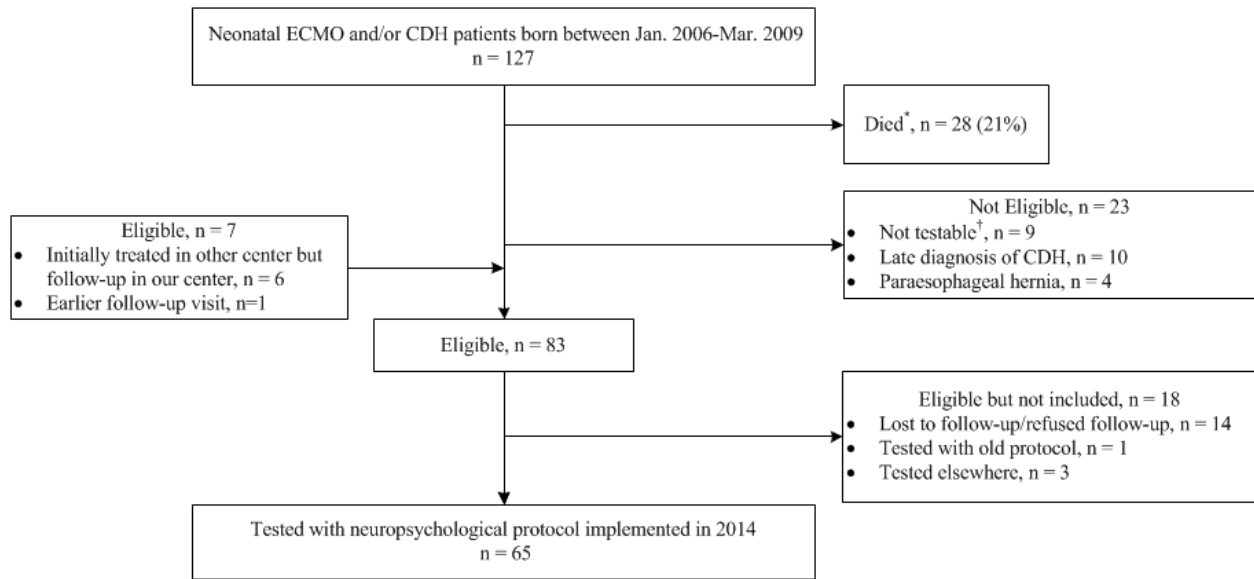
9 Please refer to the Supplemental File for a description of the tests.

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1 **Supplementary Material**



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3 **Supplemental Figure 1 Flowchart of the study population**

4 \*ECMO-other group: n = 12; ECMO-CDH-group: n = 10; CDH-non-ECMO group: n = 6.

5 † Severe neurologic or developmental impairments (n = 5; 3 patients had primary hemorrhage at cranial  
6 ultrasound performed after the ECMO run); Simpson-Golabi-Behmel Syndrome (n = 2); Down Syndrome  
7 (n = 1); Mitochondriopathy (n = 1).

8 Abbreviations: CDH = congenital diaphragmatic hernia; ECMO = extracorporeal membrane oxygenation.

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1 **Supplemental methods Description of data collection**

2 Relevant clinical data were collected at the time of hospitalization (refer to supplementary methods for  
3 description of variables). , including: gestational age, birth weight, gender, ethnicity (Dutch/ $\geq 1$  non-native  
4 Dutch parent), inborn, the need for ECMO, Pediatric Logistic Organ Dysfunction-2(PELOD-2) score(16)  
5 in the first 24 hours of pediatric intensive care unit(PICU) stay (or up to ECMO cannulation in ECMO-  
6 treated patients if ECMO was initiated in the first 24 hours of PICU stay), the maximum vasoactive-  
7 inotropic score (VIS)(17) was recorded up until ECMO cannulation for the ECMO-treated patients or up  
8 until hernia repair for the CDH-non-ECMO patients, cardiopulmonary resuscitation(CPR) during initial  
9 hospital stay, sepsis during initial hospital stay (clinical suspicion of sepsis with positive blood culture),  
10 duration of initial mechanical ventilation, ventilator-free days in the first 28 days of life, duration of PICU  
11 stay, duration of initial hospitalization, pulmonary hypertension on echocardiography during PICU  
12 admission, inhaled nitric oxide requirement, sildenafil requirement, the presence of chronic lung  
13 disease(oxygen dependency at 28 days of life)(18), and number of anesthetic procedures in the first year  
14 of life (including CDH repair and/or ECMO (de)cannulation). Additional characteristics for ECMO  
15 patients included: highest oxygenation index before ECMO, age at start ECMO, ECMO type, ECMO  
16 duration, and cranial ultrasound result before and after ECMO. Additional data for CDH patients were:  
17 diaphragmatic defect side, surgical repair technique (thoracoscopy or laparotomy), age at surgery, and  
18 patch repair requirement.

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1 **Supplemental Table 1 Patient characteristics and neuropsychological outcome at eight years of age**

<b>Supplemental Table 1. Patient characteristics and neuropsychological outcome at eight years of age</b>					
Variables	Intelligence	Sustained attention	Verbal memory immediate	Verbal memory delayed	Visuospatial immediate
<i>Univariable analyses with medical predictors</i>					
CDH-non-ECMO <sup>1</sup>	<b>B = 9.84, p = .031</b> (CI 0.96 – 18.72)	<b>B = 1.73, p = .016</b> (CI 0.34 – 3.12)	B = 0.70, p = .068 (CI -0.05 – 1.46)	B = 0.86, p = .145 (CI -0.31 – 2.02)	B = 0.31, p = .23 (CI -0.23 – 0.85)
CDH-ECMO <sup>2</sup>	<b>B = -14.11, p = .016</b> (CI -25.48 – -2.74)	B = -1.84, p = .060 (CI -0.08 – 3.76)	B = -0.73, p = .144 (CI -1.73 – 0.26)	B = -0.97, p = .204 (CI -2.48 – 0.54)	B = -0.45, p = .16 (CI -1.16 – 0.26)
ECMO-other <sup>3</sup>	B = -1.59, p = .745 (CI -11.37 – 8.19)	B = -0.77, p = .312 (CI -2.30 – 0.75)	B = -0.29, p = .475 (CI -1.11 – 0.53)	B = -0.31, p = .622 (CI -1.55 – 0.94)	B = -0.48, p = .63 (CI -0.63 – 0.67)
VA-ECMO <sup>4</sup>	<b>B = -12.59, p = .002</b> (CI -19.97 – -5.20)	B = -0.42, p = .670 (CI -2.46 – 1.61)	B = -0.38, p = .457 (CI -1.41 – 0.66)	B = -0.25, p = .677 (CI -1.47 – 0.97)	B = -0.23, p = .97 (CI -0.97 – 0.51)
Sepsis <sup>5</sup>	B = -12.36, p = .064 (CI -25.46 – 0.74)	B = -0.86, p = .451 (CI -1.42 – 3.15)	B = -0.52, p = .363 (CI -1.65 – 0.62)	B = -0.93, p = .281 (CI -2.63 – 0.78)	B = -0.23, p = .104 (CI -1.04 – 0.58)
VIS <sup>6</sup>	B = -0.08, p = .105 (CI -0.17 – 0.02)	B = -0.01, p = .217 (CI 0.01 – -0.03)	<b>B = -0.01, p = .014</b> (CI -0.02 – -0.002)	<b>B = -0.02, p = .004</b> (CI -0.03 – -0.01)	<b>B = -0.01, p = .001</b> (CI -0.01 – 0.001)
Ventilator-free days <sup>7</sup>	<b>B = 0.70, p = .006</b> (CI 0.22 – 1.19)	B = 0.07, p = .098 (CI 0.16 – -0.01)	<b>B = 0.04, p = .035</b> (CI 0.00 – 0.09)	<b>B = 0.08, p = .025</b> (CI 0.01 – 0.14)	<b>B = 0.03, p = .001</b> (CI 0.00 – 0.06)
Initial hospital stay (days)	<b>B = -0.16, p = .004</b> (CI -0.27 – -0.06)	B = -0.01, p = .133 (CI 0.00 – -0.03)	<b>B = -0.01, p = .045</b> (CI -0.02 – 0.000)	B = -0.01, p = .133 (CI -0.03 – 0.004)	B = -0.00, p = .01 (CI -0.01 – 0.01)
Anesthetics <sup>8</sup>	<b>B = -2.92, p = .027</b> (CI -5.49 – -0.35)	<b>B = -0.44, p = .036</b> (CI -0.03 – -0.85)	B = -0.15, p = .179 (CI -0.37 – 0.72)	B = -0.23, p = .175 (CI -0.57 – 0.11)	B = -0.04, p = .20 (CI -0.20 – 0.12)
<i>Univariable analyses with growth predictors</i>					
Weight-for-height z-score at 1 year	<b>B = 6.41, p = .002</b> (CI 2.48 – 10.33)	B = 0.42, p = .275 (CI -0.35 – 1.19)	B = 0.35, p = .053 (CI -0.01 – 0.69)	B = 0.29, p = .323 (CI -0.30 – 0.89)	B = 0.23, p = .03 (CI -0.03 – 0.49)
Height-corrected-for-target height z-score at 1 year	B = 0.54, p = .835 (CI -4.70 – 5.79)	B = 0.21, p = .639 (CI 0.68 – 1.10)	B = 0.28, p = .203 (CI -0.16 – 0.71)	B = 0.38, p = .287 (CI -0.33 – 1.09)	B = -0.01, p = .34 (CI -0.34 – 0.32)
Head circumference-for-age z-score at 1 year	B = 3.98, p = .060 (CI -0.18 – 8.13)	B = 0.27, p = .413 (CI -0.39 – 0.94)	B = 0.21, p = .237 (CI -0.14 – 0.55)	B = 0.23, p = .445 (CI -0.37 – 0.83)	B = 0.13, p = .14 (CI -0.14 – 0.40)
<i>Multivariable analyses</i>					
CDH-non-ECMO <sup>1</sup>	B = 7.33, p = .213 (CI -4.42 – 19.07)	B = 1.29, p = .110 (CI -2.90 – 0.31)			
CDH-ECMO <sup>2</sup>	B = -1.66, p = .851 (CI -19.51 – 16.18)				
VA-ECMO <sup>3</sup>	B = -8.03, p = .131 (CI -18.83 – 2.76)				
VIS <sup>6</sup>			B = -0.01, p = .055 (CI -0.02 – -0.000)	<b>B = -0.02, p = .026</b> (CI -0.03 – -0.002)	B = -0.01, p = .01 (CI -0.01 – 0.001)
Ventilator-free days <sup>7</sup>	B = -0.28, p = .571 (CI -1.29 – 0.72)		B = 0.02, p = .580 (CI -0.06 – 0.10)	B = 0.02, p = .555 (CI -0.06 – 0.10)	B = 0.01, p = .03 (CI -0.03 – 0.05)
Initial hospital stay (days)	B = -0.14, p = .225 (CI -0.36 – 0.09)		B = 0.00, p = .784 (CI -0.01 – 0.02)		
Anesthetics <sup>8</sup>	B = 0.40, p = .831 (CI -3.36 – 4.15)	B = 0.25, p = .285 (CI -0.22 – 0.72)			
Weight-for-height z-score at 1 year	B = 3.85, p = .180 (CI -1.88 – 9.58)				

Maternal education level, ethnicity and gender were adjusted for in all models. Growth parameters were z-scores. Variable predictors in the univariable analyses were added into the multivariable model. Only those variables found to be significant are reported. **Results** indicate significant associations at *p-value* < .05.

<sup>1</sup> CDH-non-ECMO patients were compared to patients treated with ECMO.

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<sup>2</sup> CDH-ECMO patients were compared to patients treated with ECMO following other diagnoses and to CDH patients not

<sup>3</sup> ECMO patients following other diagnosis were compared to CDH patients treated with and without ECMO.

<sup>4</sup> Patients treated with VA-ECMO were compared to patients treated with VV-ECMO.

<sup>5</sup> Sepsis during initial hospital stay (clinical suspicion of sepsis with positive blood culture).

<sup>6</sup> The maximum VIS recorded during pediatric intensive care unit stay up until ECMO cannulation for the ECMO-treated patients and for the CDH-non-ECMO patients.

<sup>7</sup> Ventilator-free days in the first 28 days of life.

<sup>8</sup> Number of anesthetic procedures in the first year of life.

Abbreviations: CDH = congenital diaphragmatic hernia; ECMO = extracorporeal membrane oxygenation; VIS = vasoactive-inotropic score; CI = confidence interval; VA-ECMO = venoarterial extracorporeal membrane oxygenation; VV-ECMO = venovenous extracorporeal membrane oxygenation.

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1 **Supplemental File 1. Descriptions of the neurodevelopmental tests.**

2 *Intelligence*

3 Wechsler Intelligence Scale for Children (WISC-III-NL)

4 The RAKIT or the Wechsler Intelligence Scale for children was used. Both tests assess verbal and non-  
5 verbal intelligence, have been shown to have good reliability and validity(1, 2), and have been used  
6 interchangeably by our group before.(3) For both tests, a normalized population mean of 100 with a  
7 standard deviation of 15 is used.(1, 2)

8

9 *Attention*

10 Dot Cancellation Test

11 This paper-and-pencil test measures sustained selective attention and concentration in terms of  
12 speed and accuracy. It consists of a paper on which figures made of three, four or five dots are  
13 displayed in 33 rows. The child is instructed to cross off all figures with four dots, as precise and  
14 as fast as they can.(4)

15

16 Stroop Color Word Test (Stroop)

17 The Stroop consists of three trials: in the first trial (Stroop 1) the subject must read color names,  
18 in the second trial (Stroop 2) name printed colors, and in the third trial (Stroop 3) name printed  
19 colors not denoted by the color name. The test can be administered to children and adults in the  
20 age range 8-65 years. Selective attention is measured with this test.(5, 6)

21

22 Trail Making Test (TMT)

1 This paper and pencil test consists of two parts. In the first part (part A), the subject must draw  
2 lines to consecutively connect numbered circles on a sheet. In the second part (part B), the  
3 subject must consecutively but alternately connect numbered and lettered circles on another  
4 worksheet. The goal of the test is to finish each part as quickly as possible. The test can be  
5 administered to children and adults in the age range 6-89 years. This test measures visual  
6 conceptual and visuomotor tracking as well as divided attention.(5, 6)

7  
8 *Verbal memory*

9 WISC-III-NL – subtest Digit Span

10 The Digit Span consists of random number sequences that increase in length and that the  
11 examiner reads aloud at the rate of 1 number per second. The child has to reproduce these  
12 numbers in the same order. Next, the sequences must be recalled backwards (3-5-7 becomes 7-5-  
13 3). The first part of the test measures short-term auditory memory and short-term retention  
14 capacity. The second part measures auditory working memory. A difference of 4 or more points  
15 between forward and backward Digit Span in favor of forward is indicative of a working-  
16 memory problem.(7)

17  
18 Rey Auditory Verbal Learning Test (RAVLT)

19 The RAVLT consists of five presentations with recall of a 15-word list, a sixth recall trial after  
20 30 minutes, and a seventh recognition trial. This test measures memory span, short- and long-  
21 term verbal memory, verbal recognition, learning curve, and retroactive or proactive  
22 interference. It can be administered to children and adults in the age range 6-89 years.(8, 9)

23

1 *Visuospatial memory*

2 Wechsler Nonverbal Scale of Ability (WNV) – subtest Spatial Span

3 The Spatial Span requires the child to touch a group of block arranged on a board in a  
4 nonsystematic manner in the same and reverse order as demonstrated by the examiner. The first  
5 part of the test measures short-term visuospatial memory and short-term retention capacity. The  
6 second part measures visuospatial working-memory.(10)

7

8 Rey Complex Figure Test (RCFT)

9 The RCFT consist of three trials. First the child has to copy a complex figure. Then after 3 and  
10 after 30 minutes the figure must be drawn from memory. Next, different figures are shown and  
11 the child has to indicate whether these figures were in the original figure. The last two trials  
12 measure short- and long-term visual-spatial memory, and visual-spatial recognition. This test can  
13 be completed by children and adults in the age range 6-89 years.(11, 12)

14

15 *Executive functioning*

16 Key Search

17 A test of strategy formation. The child is asked to demonstrate how they would search a field for  
18 a set of lost keys and their strategy is scored according to its functionality.(13)

19

20 Modified Six Elements

21 The child is asked to work on six different tasks for which they have five minutes. There are  
22 some rules the child has to obey during the task, while making sure that by the end of the five

1 minutes, all six of the tasks have been done and the child has done as much as possible of each  
2 task. This is a test of planning, task scheduling and performance monitoring.(13)

3

4 *Visual spatial processing*

5 Rey Complex Figure Test (RCFT)

6 The RCFT consists of three trials. First the child has to copy a complex figure. Then after 3 and  
7 after 30 minutes the figure must be drawn from memory. Next, different figures are shown and  
8 the child has to indicate whether these figures were in the original figure. The first trial measures  
9 visual integration. This test can be completed by children and adults in the age range 6-89  
10 years.(11, 12)

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