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Low Cerebral Oxygenation in Preterm Infants Is Associated with Adverse Neurodevelopmental Outcome

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Objective To assess whether high and low levels of cerebral oxygenation (regional cerebral oxygenation [$rScO_2$]) in infants born at <32 weeks of gestation were associated with adverse long-term outcome.

Study design Observational cohort study including preterm infants born at <32 weeks of gestation at the Wilhelmina Children's Hospital, The Netherlands, between April 2006 and April 2013. The $rScO_2$ was continuously monitored for 72 hours after birth using near-infrared spectroscopy. Outcome was assessed at 15 and 24 months of corrected age by certified investigators. An unfavorable composite outcome was defined as an outcome score below -1 SD or death. Various $rScO_2$ thresholds were explored.

Results In total, 734 infants were eligible for analysis, 60 of whom died. Associations with an unfavorable cognitive outcome in multivariable analysis were comparable for time spent with a $rScO_2$ below 55% and -1.5 SD (according to published reference values), with an OR of 1.4 (CI 1.1-1.7) for 20% of time below either threshold. Results at 15 months were comparable with results at 24 months. Results were not statistically significant for thresholds defining high values of $rScO_2$. The composite motor outcome was not significantly related to either low or high values or $rScO_2$.

Conclusions Low, but not high, $rScO_2$ was associated with an unfavorable cognitive outcome. This suggests the use of a threshold of $rScO_2$ <55% for future clinical studies when using adult near-infrared sensors ($rScO_2$ <65% for neonatal sensors, approximately). *(J Pediatr 2019;207:109-16).*

Survival of infants born preterm has increased dramatically over the last decades. The incidence of brain injury, however, is still high. Known entities are peri- and intraventricular hemorrhage, associated posthemorrhagic ventricular dilatation, white matter injury, and cerebellar lesions. Although their pathophysiology has not been completely resolved, the development of these lesions seems to be at least partially related to disturbances in cerebral blood flow and oxygenation.[1,2]

Traditionally, the well-being of infants is assessed by monitoring arterial oxygen saturation, heart rate, and blood pressure. Although these have a clear association with the cardiorespiratory status of a patient, neither of them directly depicts blood flow or oxygenation at the level of the end-organs (eg, the brain).[3] Near-infrared spectroscopy (NIRS) can provide information on end-organ perfusion and oxygenation by providing a direct, continuous, and absolute estimate of the tissue oxygen saturation (regional cerebral oxygenation [$rScO_2$]).[4-6] A recent randomized trial demonstrated that the cerebral oxygenation could be stabilized by combining commercially available NIRS devices with an intervention guideline.[7,8] Although indices of cerebral oxygenation as obtained by NIRS have been associated both with short-term and more long-term outcome, the impact of these results are limited because of heterogeneous study designs and relatively small sample sizes.[9-11] To transform NIRS from a predominantly research tool and trend monitor to an established clinical monitoring tool, reliable thresholds of cerebral oxygenation should be defined that are associated with clinically relevant outcomes.

The 2 primary aims of this study were to determine whether the pattern of $rScO_2$ was different between infants with and without adverse neurodevelopmental outcome and to investigate whether thresholds of $rScO_2$, quantifying both hypo- and hyperoxia were related to adverse neurodevelopmental outcome. We hypothesized that both hypo- and hyperoxygenation of the brain would be associated with adverse neurodevelopmental outcome.[9-14]

Methods

This study is part of an ongoing prospective observational cohort study that aims to record physiologic variables during the first 72 hours after birth in all infants born with a gestational age of <32 weeks who are admitted to the level III neonatal

Bayley-III	Bayley Scales of Infant and Toddler Development, Third Edition
GMDS	Griffiths Mental Development Scales
NIRS	Near-infrared spectroscopy
ROC	Receiver operator characteristics
$rScO_2$	Regional cerebral oxygenation
SES	Socioeconomic status

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intensive care unit of the Wilhelmina Children's Hospital, Utrecht, The Netherlands. The ethics committee of the University Medical Center Utrecht, which adheres to the Medical Research Involving Human Subjects Act, approved the use of anonymized data (protocol 14-335/C). Data collection was attempted in 835 infants between April 2006 and April 2013. Lost to follow-up was defined as having neither 15 nor 24 months neurodevelopmental outcome data available. Subjects did not participate in the SafeBoosC trial.[7]

Data Collection and Processing

The methods of data collection are reported in more detail elsewhere.[15] Clinical variables were used to calculate CRIB II scores.[16] Based on the infants' zip code, data on the socioeconomic status (SES) of the family was obtained from the Central Bureau of Statistics (The Hague, The Netherlands, www.cbs.nl). The SES is expressed as a z score that combines information on the parents' highest educational degree, total household income, and profession into a single score. Higher scores indicate lower SES.

Arterial oxygen saturation, invasive blood pressure, and heart rate were monitored using a patient monitor (IntelliVue MP70; Philips Healthcare, Best, The Netherlands). The $rScO_2$ was monitored by using a 2-wavelength (ie, 730 and 810 nm) NIRS monitor (INVOS 4100 or 5100c; Medtronic, Minneapolis, Minnesota) in combination with a small adult sensor (SomaSensor SAFB-SM; Medtronic). A patent ductus arteriosus confirmed to be hemodynamically significant on cardiac ultrasound was either treated with indomethacin or surgically closed.[17] The $rScO_2$ was one of the clinical variables used to prompt cardiac ultrasound, but clinical interventions were not based on the $rScO_2$.

Data was analyzed with in-house developed software (SignalBase; University Medical Center Utrecht, The Netherlands). Before analysis, artifacts were removed manually by a single author. Thereafter, 1-hour periods were selected during the first 72 hours after birth (ie, postnatal age). Before statistical analysis, 1-hour periods containing less than 10 minutes of data were rejected.

Neurodevelopmental Outcome

Assessment of neurodevelopmental outcome was performed by certified investigators at 15 and 24 months of age, corrected for prematurity. At 15 months the Griffiths Mental Development Scales (GMDS) were used.[18] At 24 months, the Bayley Scales of Infant and Toddler Development, Third Edition (Bayley-III) was used for all neonates with a gestational age of <30 weeks or a birthweight of <1000 g, otherwise the GMDS was used.[18-21]

Statistical Analyses

Composite outcomes were used, and an unfavorable outcome was defined as a neurodevelopmental test score <−1 SD below the mean or death. The Bayley-III provides separate estimates for cognitive and motor outcome, where GMDS does not.[18,19] For the cognitive outcome at 24 months of corrected age, either the Bayley-III cognitive composite score (mean 100, SD 15) or the GMDS DQ (excluding the locomotion subscale, mean 100, SD 12) was used.[18-21] For the motor outcome at 24 months, either the Bayley-III gross motor score (mean 10, SD 3) or the GMDS locomotion subscale (mean 100, SD 16) was used.[18-21] When both GMDS and Bayley-III were available, only the Bayley-III scores were used. To ensure methodological consistency with the 24-month data, outcomes at 15 months were also divided into cognitive (GMDS excluding the locomotor subscale) and motor outcomes (GMDS locomotion subscale).

All statistical analyses were performed in R for Windows 64-bit, v 3.4.3 (R Core Team, R Foundation for Statistical Computing, Vienna, Austria). A mixed-model approach was used to assess the course of $rScO_2$, with adverse outcome (yes/no) as a fixed factor.[15]

The $rScO_2$ was related to various thresholds defining hypoxia and hyperoxia, and expressed as percentage of time with a $rScO_2$ spent above/below/inside/outside these thresholds: fixed thresholds ranging 30%-90% in steps of 5% $rScO_2$ from one threshold to another (eg, <30%, <35%, <40%, etc, and >90%, >85%, >80%, etc); time spent with $rScO_2$ outside 55%-85% limits (ie, <55% and >85% combined)[7,8]; time spent in $rScO_2$ quartiles derived from the current dataset[10]; thresholds ranging (−2 SD to +2 SD) in 0.5 SD steps (eg, <−2 SD, <−1.5 SD etc, >2 SD, >1.5 SD etc, and outside ±2 SD, ±1.5 SD etc), based on $rScO_2$ reference values.[15]

The SafeBoosC trial definition for hypoxia/hyperoxia, time in seconds, and area under the curve were only available for analysis in fixed thresholds.[7,8] To determine the threshold that was most strongly associated to outcome, first a preselection was made based on visual inspection of box and whisker plots, which were subsequently tested (Mann-Whitney U test or Student t test, where applicable). Second, univariable logistic regression models were compared based on the Akaike information criterion and log likelihood. Third, receiver operator characteristics (ROC) analysis was applied to determine which thresholds had the best association with outcome. Finally, multivariable logistic regression analysis was performed including variables listed in **Table I**, where gestational age, birth weight <10th percentile, SES z score, and type of follow-up at 24 months (ie, GMDS or Bayley-III) were always included as covariates. Data are presented as either mean ±SD, median with IQR, counts (%), or OR with 95% CI. A *P* value of <.05 was considered statistically significant.

Results

Chromosomal/congenital abnormalities and data corruption caused exclusion of 32 patients. A total of 69 patients were lost to follow-up (**Figure 1**; available at www.jpeds.com). Data from 734 infants was available for analysis, 60 of whom died. **Table I** shows the baseline characteristics and follow-up details. Clinical characteristics were not significantly different for infants who were lost to follow-up. Artifact rejection rates were unrelated to gestational age and <2% of total data in all cases.

A quadratic model with autoregressive first order correlation structure provided the best fit for modeling $rScO_2$ over

Table I. Clinical characteristics and follow-up

	Total	24-25 wk	26-27 wk	28-29 wk	30-31 wk
Variables	**n = 734**	**n = 90**	**n = 186**	**n = 231**	**n = 227**
Clinical variables					
Sex (n, male / female)	399/335	51/39	100/86	124/107	124/103
Gestational age (wk, mean [SD])	28.5 [2.0]	25.1 [0.6]	27.0 [0.6]	28.9 [0.56]	30.7 [0.55]
Birth weight (g, mean [SD])	1130 [331]	771 [112]	925 [182]	1194 [241]	1374 [339]
Birth weight z score (mean, [SD])	0.03 [0.93]	0.42 [0.86]	0.01 [0.86]	0.15 [0.89]	–0.23 [0.97]
Mechanical ventilation (d 1/2/3, %)	367 (50%) / 374 (51%) / 390 (53%)	74 (82%) / 73 (81%) / 72 (80%)	130 (70%) / 127 (68%) / 119 (64%)	101 (44%) / 101 (44%) / 96 (42%)	62 (27%) / 59 (26%) / 55 (24%)
Apgar score 1/5 min (med, [IQR])	7 [5-8] / 8 [7-9]	5 [3-6] / 7 [6-8]	6 [4-8] / 8 [6-9]	7 [5-8] /8 [8-9]	7 [6-8] /9 [8-9]
Antenatal corticosteroids, full course (n, %)	557 (76 %)	69 (76.7%)	136 (73.1%)	180 (77.9%)	272 (75.8%)
Patent ductus arteriosus (n, %)	230 (31.1%)	64 (71.1%)	87 (46.8%)	56 (24.2%)	23 (10.1%)
Culture proven sepsis (n, %)	193 (26.0%)	38 (42.3%)	60 (32.3%)	51 (22.0%)	44 (19.4%)
Intraventricular hemorrhage (n, %)	223 (31.2%)	45 (50.0%)	63 (33.9%)	64 (27.7%)	51 (22.5%)
- Grade I/II	152 (20.6%)	29 (32.4%)	32 (17.2%)	52 (22.5%)	39 (17.2%)
- Grade III/IV	71 (10.6%)	16 (17.8%)	31 (16.7%)	12 (5.2%)	12 (5.3%)
CRIB II score (med, [IQR])	9 [6-11]	8 [6-12]	9 [7-12]	9 [7-11]	8 [6-11]
Died in hospital /<7d / <14d (n, %)	60 (8.2%) / 21 (2.9%) / 34 (4.6%)	24 (26.7%) / 4 (4.4%) / 10 (11.1%)	22 (11.8%) / 10 (5.4%) / 16 (8.6%)	10 (4.3%) / 5 (2.2%) / 6 (2.6%)	4 (1.8%) / 2 (0.9%) / 2 (0.9%)
Follow-up variables					
15 mo of corrected age (med, [IQR])	15.8 [15.3-17.4]	15.9 [15.4-16.6]	15.7 [15.2-16.5]	15.6 [15.2-16.6]	16.8 [15.4-18.5]
GMDS DQ (mean, [SD])	102.2 [9.3]	100.2 [11.2]	102.1 [9.0]	103.7 [8.7]	101.7 [9.2]
24 mo of corrected age (mean, [SD])	24.7 [2.4]	24.3 [0.6]	24.1 [0.5]	24.2 [1.3]	24.9 [2.5]
GMDS DQ (mean, [SD])	97.0 [9.3]	n/a	n/a	99.3 [6.7]	96.8 [8.7]
GMDS DQ excl. locomotor	97.1 [9.4]	n/a	n/a	99.7 [7.3]	97.0 [8.8]
GMDS DQ locomotor only	96.4 [11.1]	n/a	n/a	99.4 [9.9]	96.1 [10.3]
Bayley-III-NL cognition (mean, [SD])	102.2 [14.0]	99.5 [16.1]	102.1 [13.4]	104.1 [13.6]	99.6 [13.8]
Bayley-III-NL total motor (mean, [SD])	108.4 [12.1]	105.4 [12.7]	107.7 [12.6]	110.5 [11.0]	107.3 [12.0]
Bayley-III-NL gross motor (med, [IQR])	10 [9-12]	10 [8-12]	10 [9-12]	10 [9-12]	10 [8-11]
SES z score (mean, [SD])	–0.09 [1.06]	–0.17 [1.04]	0.04 [1.10]	–0.08 [1.02]	–0.19 [1.07]
Eligible with NIRS (n) live (n, %)	803 / 743 (92.5%)	92 / 68 (73.9%)	202 / 180 (89.1%)	243 / 233 (95.9%)	266 / 262 (98.5%)
- Alive loss to follow-up (n, %)	69 (9.3%)	2 (2.9%)	16 (8.9%)	12 (5.2%)	39 (14.9%)
Outcome data (n, % of eligible and alive)	674 (90.7%)	66 (97.1%)	164 (91.1%)	221 (94.8%)	223 (85.1%)
-15 mo GMDS	658 (88.6%)	64 (94.1%)	164 (91.1%)	217 (93.1%)	222 (84.7%)
-24 mo total/Bayley III-NL/GMDS	559 (75%) / 453 (61%) / 106 (14%)	61 (90%) / 61 (90%) / -	160 (89%) / 160 (89%) / -	202 (87%) / 181 (78%) / 21 (9%)	136 (52%) / 51 (19%) / 85 (32%)

BSITD-III-NL, Bayley Scaled of Infant and Toddler development III, Dutch edition; *CRIB*, Clinical Risk Index for Babies; *DQ*, developmental quotient; *NL*, Netherlands.

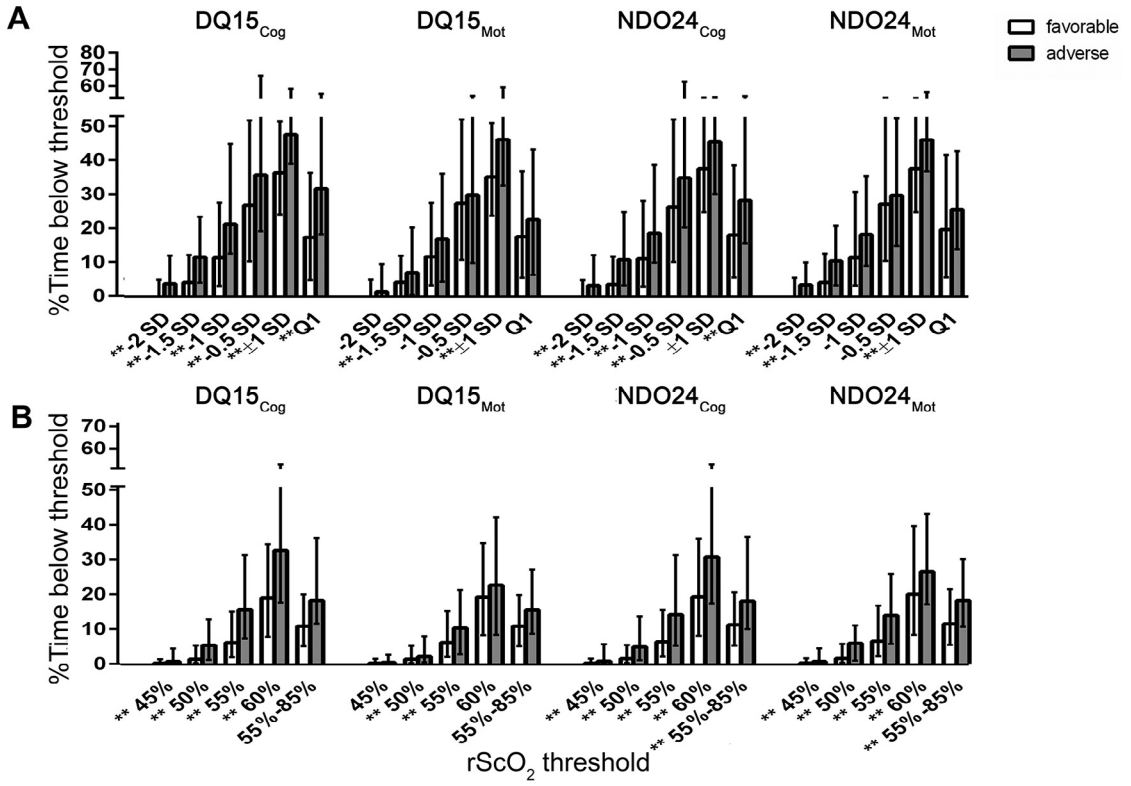

Figure 3. The percentage of **A,** time spent below and outside thresholds based on published reference values, and **B,** time spent below or outside fixed thresholds during 0-72 hours after birth for outcomes at 15 and 24 months of corrected age. Q1, time spent with $rScO_2$ in the lowest quartile based on the current data set. ** Indicates statistical significance based on Mann-Whitney U test or Student t test, where applicable.

the first 72 hours after birth (**Figure 2**; available at www.jpeds.com). Infants with adverse composite cognitive outcomes at 24 months had a lower $rScO_2$ overall (coefficient −1.9%, 95% CI −3.3 to −0.49). This did not change over time (ie, no interaction). No significant associations with motor outcome were found (**Table II**; available at www.jpeds.com).

Figure 3 displays the subset of thresholds that remained after visual preselection. In logistic regression analysis, the percentage of time spent with $rScO_2$ <55% provided the best model fit in relation to cognitive adverse outcome (**Table III**). The median burden of hypoxia, according to the SafeBoosC trial definition, for $rScO_2$ <55% was 18.5% of hours (IQR 5.5%-56.1%) vs 42.3% of hours (12.2-101.2) for the favorable and adverse cognitive outcome groups, respectively.[7,8] Although model fits were statistically different (χ^2 $P < .001$) between the 3 thresholds (ie, <55%, <−1 SD, and <−1.5 SD), differences in log likelihood and the Akaike information criterion were <2. The ROC area under the curve for the time <55% (65.5%, CI 60.2%-70.8%, **Figure 4** [available at www.jpeds.com]) and <−1.5 SD (63.7%, CI 58.4-69.1%) were not different ($Z = 1.36$, $P = .17$). For time <−1 SD (61.5%, CI 56.1%-66.8%) the area under the curve was significantly lower ($Z = 4.00$, $P < .001$). Time(s), area, and SafeBoosC burden <55% did not provide greater ROC area under the curve.

For composite motor outcome, logistic regression analysis was significant at 15 months over 0-72 hours for $rScO_2$ <55%, time spent outside ±1.0 SD, and time spent outside ±1.5 SD. The latter providing the best model fit (OR 1.017, CI 1.008-1.026) and ROC AUC (62.4%, CI 57.6%-67.2%). Thresholds quantifying elevated levels of oxygenation were not significantly associated with outcome. Except for time spent outside ±1.0 SD and ±1.5 SD in association with neurodevelopmental outcome at 15 months, time spent outside various ranges never provided a better model fit than time below the lower boundary of that threshold (eg, <−1.0 SD, <−1.5 SD).

Results of multivariable analysis for composite cognitive scores are presented in **Table IV**. In an identical multivariable analysis, now only including infants <28 weeks of gestational age, the OR for percentage of time spent <55% in association with composite cognitive outcome at 24 months was 1.019 (95% CI 1.003-1.035). Multivariable analysis of motor outcome yielded no statistically significant results (data not shown).

Discussion

Cerebral oxygen saturation of <55% measured by NIRS during the first 3 days after birth is associated with unfavorable cognitive outcome. Thresholds quantifying high $rScO_2$ were not found to be significantly associated with outcome. The strength of this study lies in the size of the study population, and the fact that $rScO_2$ was measured continuously over the first 72

Table III. Results from univariable logistic regression analysis for cognitive outcome

Data obtained by NIRS*

	Composite cognitive outcome 24 mo of corrected age			Composite cognitive outcome 15 mo of corrected age		
Period	Threshold	OR	95% CI	Threshold	OR	95% CI
0-72 h	<55%	1.024	(1.011-1.036)	<55%	1.027	(1.013-1.040)
Day 1	<55%	1.014	(1.005-1.022)	<55%	1.016	(1.007-1.026)
Day 2	<55%	1.004	(1.002-1.005)	±1.5 SD†	1.008	(0.998-1.017)
Day 3	<55%	1.019	(1.009-1.029)	±1 SD†	1.017	(1.008-1.026)
Clinical variables						
		OR	**95% CI**		**OR**	**95% CI**
Gestational age (wk)	—	0.770	(0.691-0.855)	—	0.697	(0.622-0.778)
Lower SES (z score)	—	1.282	(1.070-1.535)	—	1.169	(0.960-1.417)
Birth weight <10th % (yes/no)	—	1.407	(0.780-2.436)	—	1.402	(0.712-2.582)
Grade III/VI IVH (yes/no)	—	4.626	(2.785-7.655)	—	4.584	(2.649-7.821)
Mech. vent.0-72 h (yes/no)	—	2.796	(1.801-4.464)	—	3.852	(2.351-6.597)
Antenatal corticosteroids full course (yes/no)	—	0.657	(0.431-1.014)	—	0.614	(0.393-0.972)
Apgar score 5 min	—	0.766	(0.685-0.855)	—	0.699	(0.623-0.782)
Female (yes/no)	—	0.675	(0.451-1.002)	—	0.464	(0.291-0.724)
hsPDA (yes/no)	—	2.359	(1.591-3.503)	—	2.357	(1.539-3.611)
Sepsis (yes/no)	—	1.353	(0.887-2.039)	—	1.397	(0.881-2.180)
CRIB-II score	—	0.969	(0.917-1.023)	—	0.992	(0.934-1.053)

hsPDA, hemodynamically significant patent ductus arteriosus; *IVH*, intraventricular hemorrhage.
*OR relates to 1% change (eg, 10% of time spend <55% 0%-72% yields OR 1.24 for composite adverse outcome at 24 months of corrected age.
†Time spent outside SD boundaries according to published reference values.

hours. The close competition between <55%, <−1 SD, and <−1.5 SD is not surprising, as the average −1.5 SD over all gestational ages on day 1 and 3 comes down to 55%-56%.[15]

Values below 50% have previously been reported to be associated with neurodevelopmental outcomes.[9,10] Interestingly, both studies used different sensors (ie, adult and pediatric sensors), which are known to differ ~10% in values.[22-24] A $rScO_2$ of <50% recorded using pediatric sensors[10] translates to $rScO_2$ ~40% in our data obtained using adult sensors. This difference may explain the lack of association between $rScO_2$ of <50% and cognitive outcomes in their dataset, as values $rScO_2$ of <40% using adult sensors are rare in newborn infants.[15] Their data supports this, as the duration of $rScO_2$ <50% recorded with pediatric sensors on day 1 was only 1 minute.[10] The threshold of 55% reported here has been shown to make sense from a physiologic perspective, with a $rScO_2$ >55% preventing low lactate and adenosine triphosphate levels in animal models.[25] A randomized trial, using the <55% and >85% thresholds

Table IV. Multivariable logistic regression

Adverse composite cognitive outcome 24 mo of corrected age

	$rScO_2$ <55%		$rScO_2$ < −1.5 SD	
Variables	Odds-ratio	95% CI	Odds-ratio	95% CI
Time below threshold 0-72 h (%)*	1.018	(1.001-1.034)	1.017	(1.001-1.032)
Gestational age (wk)	0.940	(0.771-1.149)	0.903	(0.743-1.099)
Lower SES (z score)	1.504	(1.182-1.916)	1.506	(1.184-1.917)
Birth weight <10th % (yes/no)	3.938	(1.841-8.194)	3.819	(1.790-7.918)
Grade III/VI IVH (yes/no)	2.543	(1.138-5.339)	2.388	(1.073-4.990)
Mechanical ventilation 0-72 h (yes/no)	1.863	(1.016-3.513)	1.795	(1.001-3.377)
Assessment (1 = GMDS, 2 = Bayley-III)	0.484	(0.217-1.095)	0.471	(0.210-1.067)
Adverse composite cognitive outcome 15 mo of corrected age				
Time below threshold 0-72h (%)*	1.023	(1.010-1.037)	1.021	(1.007-1.034)
Gestational age (wk)	0.810	(0.707-0.924)	0.773	(0.676-0.880)
Lower SES (z score)	1.110	(0.889-1.381)	1.121	(0.899-1.393)
Birth weight <10th % (yes/no)	3.161	(1.464-6.542)	3.033	(1.411-6.247)
Grade III/VI IVH (yes/no)	3.241	(1.757-5.911)	3.109	(1.695-5.634)
Mechanical ventilation 0-72 h (yes/no)	1.959	(1.100-3.597)	1.909	(1.074-3.496)
Apgar score 5 min	0.791	(0.694-0.903)	0.786	(0.690-0.897)
Female (yes/no)	0.459	(0.274-0.752)	0.496	(0.298-0.807)

*Relates to 1% of time, eg, OR 1.018 with 20% of time spent <55% yields OR 1.36.

reported no neurodevelopmental benefit of cerebral oximetry. However, these results should be interpreted with caution as it was not powered for long-term outcomes.[26]

Low $rScO_2$ reflects low oxygenation but is also indicative of marginal cerebral blood flow.[5,27] The effects of hypoxia(-ischemia) on the developing brain can be related to direct loss of tissue, either macroscopic (ie, cystic periventricular leukomalacia [PVL] and periventricular hemorrhagic infarction) or microscopic, and disrupted maturation and regeneration of various progenitor cells (eg, immature neurons, glial cells, pre-oligodendrocytes).[28-30] The latter is the predominant entity nowadays due to decreased occurrence of cystic PVL.[31] It is well known that preterm birth is associated with measures of brain maturation and neurodevelopmental outcome, and measures of cerebral oxygenation have in turn been related to indices of brain maturation such as gray matter volume and gyrification index.[32,33]

For hyperoxia, the presumed mechanism leading to brain damage is oxidative stress in the absence of adequate antioxidative countermeasures, which is particularly harmful for preoligodendrocytes.[2,13,34] We could not confirm our hypothesis that hyperoxygenation was independently associated with outcome.[12,35] However, the fact that time outside ±1.5 SD/ ±1 SD thresholds had the strongest association with cognitive (**Table III**, day 2 + 3) and motor outcome at 15 months, compared with <−1.5 SD or <−1 SD, suggests an additive adverse effect of hyperoxia. Although speculative, for motor outcome this could be explained by the specific sensitivity to hyperoxia of the cerebellum.[36] Moreover, the number of episodes and hyperoxia for prolonged periods of time might be more relevant than total time of hyperoxia.

Counterintuitively, when analyzing the fixed thresholds, in virtually all cases the percentage of time and not the area under/above the curve had the strongest association with outcome. This suggests the existence of an all or nothing threshold above/below which cellular mechanisms fail after a certain duration of time, and indicates that the number and duration of hypoxia/hyperoxia episodes is worth exploring. Unfortunately, software restrictions prohibited such an analysis at this time. The suggestion that the duration of hypoxia is important to analyze is supported by experimental work showing that mild intermittent hypoxia might be neuroprotective by a mechanism referred to as preconditioning, whereas severe intermittent hypoxia clearly has detrimental effects.[37-40]

There were some limitations to our study. First, the Bayley-III is known to have an upward bias compared with Bayley-II, to counter this, normative values for the Dutch population were used.[20,41,42] The use of both the Bayley-III and GMDS could be a source of attrition bias. The outcome data were normalized and dichotomized to prevent bias, and mode of assessment was always included in multivariable analysis (**Table IV**, OR not significant). Moreover, associations with outcome at 15 months mirror those at 24 months, indicating low attrition bias. A source of selection bias is selective loss to follow-up of infants >30 weeks of gestational age, especially at 24 months. The lack of significant clinical differences of infants lost to follow-up, comparable results at 15 and 24 months, and similar but stronger associations when selectively analyzing infants <28 weeks of gestational age suggest this was not a major source of bias. Third, although ORs presented here are low, one needs to keep in mind that these are displayed as percentage of time. The upper quartile in the adverse outcome group at 24 months (ie, 31.4% of time $rScO_2$ <55%) would yield an OR 1.6 (CI 1.16-2.02). In addition, we chose to model both $rScO_2$ and intraventricular hemorrhage grade III/IV separately, the latter having a considerably higher OR. Hypoxia (low $rScO_2$) could be considered part of the causative chain of peri- and intraventricular hemorrhage[11,17,43,44] and indeed a $rScO_2$ of <55% was significantly association with grade III/IV hemorrhages (OR 1.017; CI 1.007-1.026, gestational age corrected). Finally, strengths and limitations of NIRS have been reported elsewhere.[45] Improved precision of newer NIRS devices would reduce the number of patients needed in interventional trials.[46-49]

The question remains whether we can improve outcome by intervening on $rScO_2$. Results of the SafeBoosC trial suggest that the use of NIRS can reduce the burden of hypoxia.[7] Ideally, these results need to be replicated in a validation set preferably by using a single method of assessment of neurodevelopmental outcomes, and including advanced magnetic resonance imaging (eg, brain volumes, cortical folding).[50,51] Future studies should include the number and duration periods with $rScO_2$ above/below a certain threshold. A NIRS white paper and a clear context of use could facilitate implementation and should include a treatment guideline including various clinical variables (eg, respiratory support, CO_2, blood pressure) and time to expected effect on $rScO_2$.[8] Finally, a large trial is needed that is sufficiently powered on clinically relevant outcomes including long-term outcomes, bearing in mind the thresholds reported here.

Levels of cerebral oxygenation of <55% (as measured using adult probes) had the strongest association with composite cognitive outcome at 24 months of corrected age. The association with $rScO_2$ <−1.5 SD according to recently published reference values was comparable.[15] Isolated high values of $rScO_2$ were not independently associated with an adverse outcome. This study confirms that the threshold of $rScO_2$ for future research should be <55% when measured with adult probes and <65% (approximately) when measured with neonatal/pediatric sensors. ■

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50 Years Ago in *The Journal of Pediatrics*

Ankylosing Spondylitis with Childhood Onset

Schaller J, Bitnum S, Wedgwood RJ. J Pediatr 1969:74:505-16

Schaller et al provide a thorough description of symptoms, signs, and course of 7 children (all male) with early-onset ankylosing spondylitis before the age of 12 years. All had a classic presentation but only 2 were diagnosed before 18 years of age. Three presented with inflammatory low back (worse at rest), hip, groin, and buttocks pain. Four presented with peripheral arthritis, of whom 3 developed sacroiliac joint and back symptoms within 4 years of onset. One patient seemed to have heel enthesitis at onset. The loss of mobility of the lumbodorsal spine was documented in 4 patients before the age of 18 years. All patients developed substantial sacroiliac radiologic changes and 6 also had spinal findings, mainly lumbar, but also more proximal in 4 patients. It is important to note that none of the children had radiologic findings at onset underlying the late development of sacroiliac joint radiologic changes and that normal plain radiographs do not exclude this diagnosis. Systemic symptoms were not prominent, except for 1 patient who had severe anemia with possible underlying inflammatory bowel disease. Four children had mild residual functional disabilities, 1 moderate and 2 severe. Patients were treated with nonsteroidal anti-inflammatory drugs, mainly indomethacin (preferred) or phenylbutazone, with good symptomatic (pain) effect, but the radiologic and functional outcomes, as noted, were poor. Gold therapy and corticosteroids were not effective.

Although the symptoms and natural history of this type of arthritis have not changed over the last 50 years, all else has changed. First, the name of this entity was changed to enthesitis-related arthritis, to reflect the unique involvement of the enthesis especially in children, and it is included as one of the subtypes of juvenile idiopathic arthritis. Much has been learned regarding the etiology, genetics, and pathogenesis, especially via the strong association with HLA B27. Early diagnosis is now possible through use of magnetic resonance imaging of the sacroiliac joint and ultrasound examination of the peripheral enthesis. Treatment has been revolutionized through the use of tumor necrosis factor inhibitors and, in adults and perhaps soon in children, IL-17 inhibitors, which can impact the clinical and radiologic disease progression of this potentially devastating and debilitating disease as outlined by Schaller et al.

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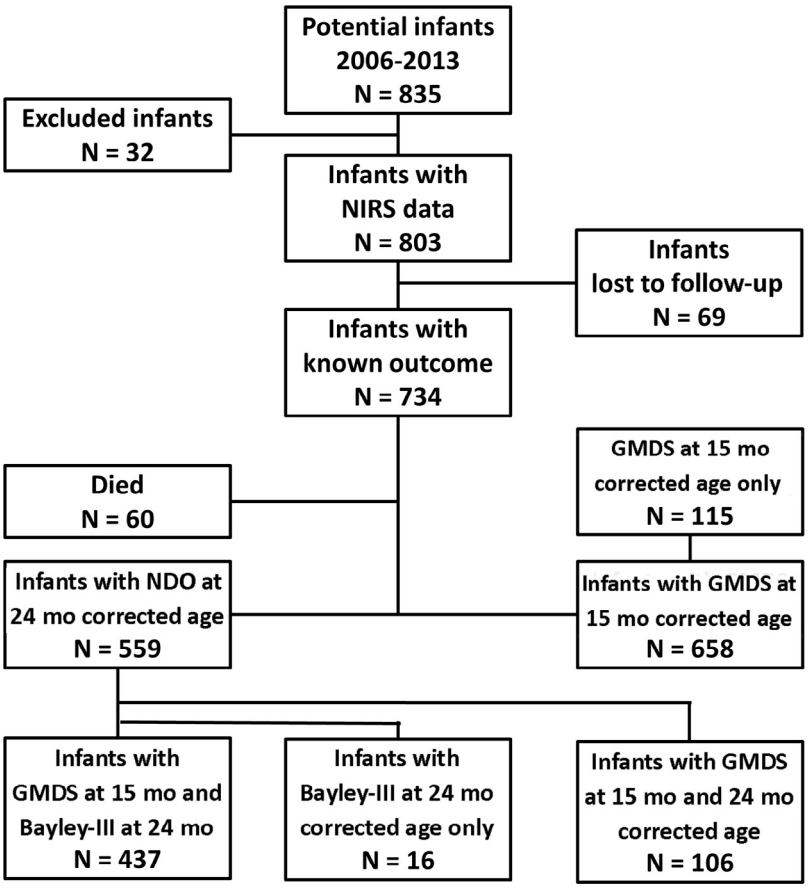

Figure 1. Flow chart of included patients. *NDO*, neurodevelopmental outcome.

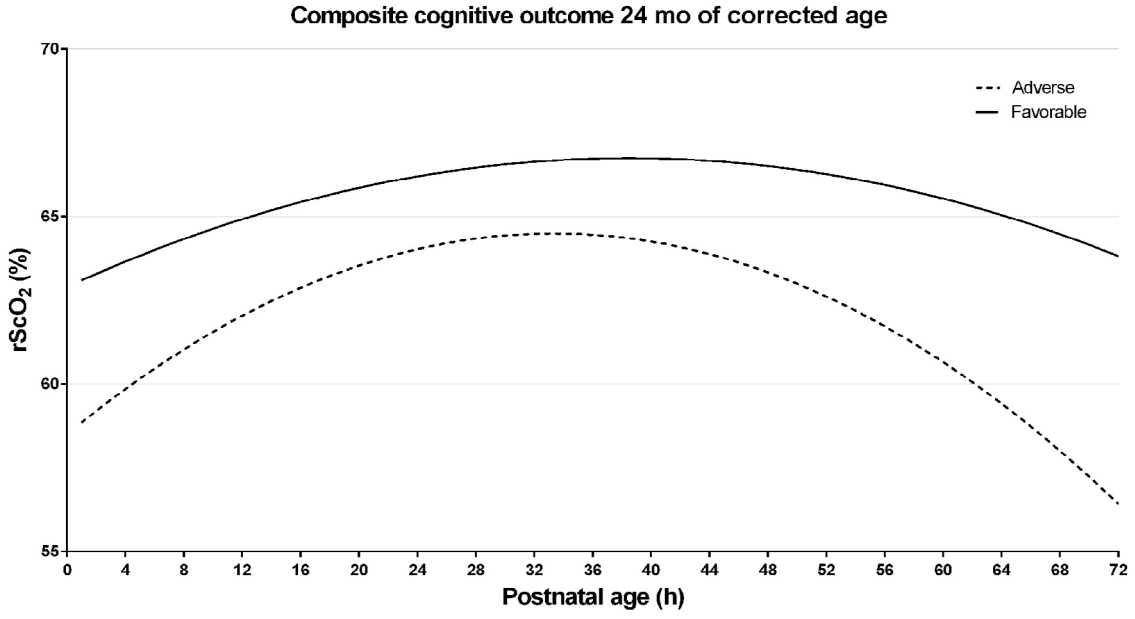

Figure 2. The model fit of the course of the $rScO_2$ over time plotted for infants with adverse and favorable outcome.

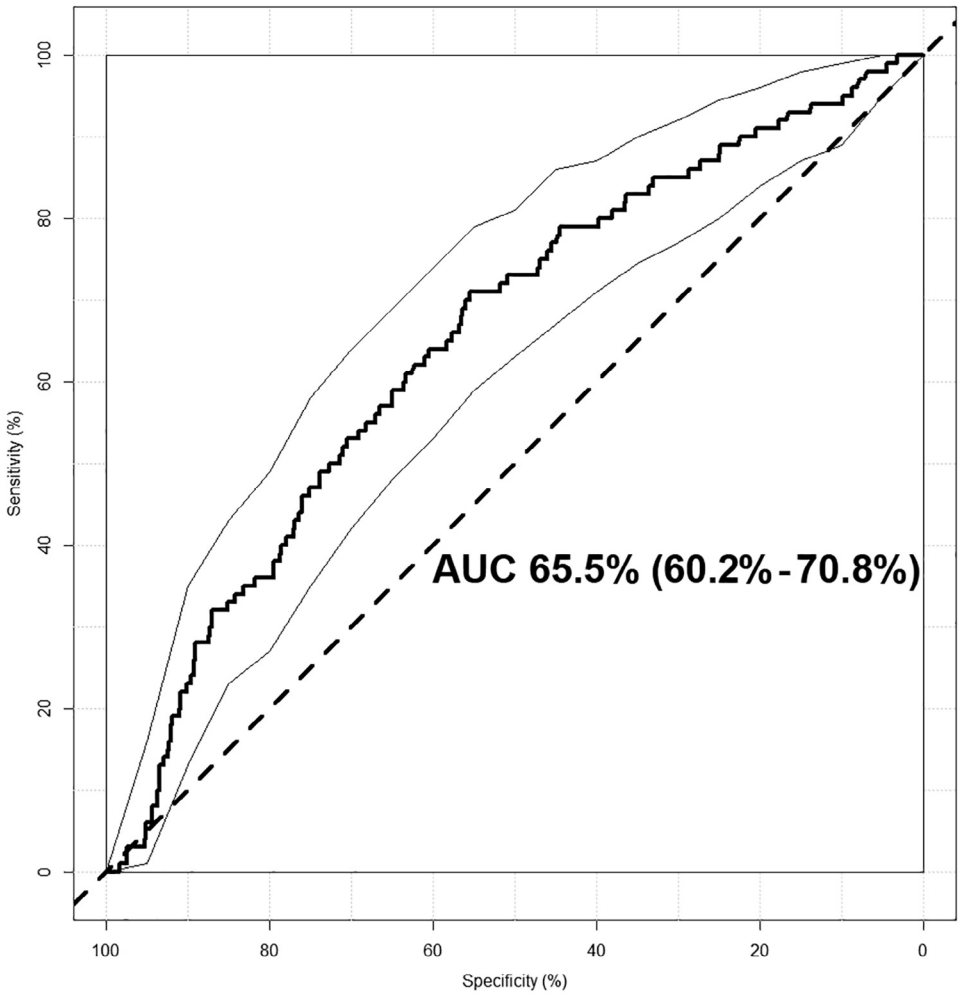

Figure 4. ROC curve with 95% CI for time spent <55% 0-72 hours after birth with composite cognitive outcome at 24 months of corrected age. *AUC*, area under the curve.

Table II. Results of mixed-effects modeling

	Cognitive outcome 24 mo of corrected age <–1 SD or death			Cognitive outcome 15 mo of corrected age <–1 SD or death		
Variables	**Lower bound**	**Estimate**	**Upper bound**	**Lower bound**	**Estimate**	**Upper bound**
Intercept	62.59	63.50	64.41	62.93	63.78	64.62
PA(h)	0.18	0.22	0.25	0.17	0.20	0.24
$PA(h)^2$	–0.0031	–0.0026	–0.0021	–0.0029	–0.0024	–0.0020
Adverse outcome	–3.26	–1.88	–0.49	–3.56	–1.98	–0.40
	Motor outcome 24 mo of corrected age <–1 SD or death			**Motor outcome 15 mo of corrected age <–1 SD or death**		
	Lower bound	**Estimate**	**Upper bound**	**Lower bound**	**Estimate**	**Upper bound**
Intercept	62.28	63.19	64.09	62.74	63.61	64.48
PA(h)	0.18	0.22	0.25	0.17	0.20	0.24
$PA(h)^2$	–0.0031	–0.0026	–0.0021	–0.0029	–0.0024	–0.0020
Adverse outcome	–1.31	0.24	1.78	–1.32	–0.18	0.96

PA, postnatal age.