Neurodevelopmental Outcomes after Premedication with Atropine/Propofol vs Atropine/Atracurium/Sufentanil for Neonatal Intubation: 2-Year Follow-Up of a Randomized Clinical Trial

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This study followed 173 newborn infants in the PREmedication Trial for Tracheal Intubation of the NEOnate multicenter, double-blind, randomized controlled trial of atropine-propofol vs atropine-atracurium-sufentanil for premedication before nonemergency intubation. At 2 years of corrected age, there was no significant difference between the groups in death or risk of neurodevelopmental delay assessed with the Ages and Stages Questionnaire.

Trial registration Clinicaltrials.gov: NCT01490580. *(J Pediatr 2021;231:273-7).*

Premedication for nonemergent tracheal intubation in newborn infants is strongly recommended to decrease pain and adverse events related to the procedure.[1] However, there is no consensus on which drugs to use.[1-3] A short-acting opioid associated with a muscle-blocker is recommended by several academic societies[2,3] but prevents titration and assessment of proper sedation and analgesia.[4] Propofol is a short-acting anesthetic that has been proposed as an alternative.[1,5,6] Reported advantages of propofol are preservation of spontaneous ventilation, less frequent oxygen desaturation, possible titration, and faster intubation.[4-6] However, there are concerns about potential neurologic adverse effects of propofol in newborn infants related to the risk of systemic hypotension[7,8] and neurotoxicity observed in animals.[9]

The PRETTINEO (PREmedication Trial for Tracheal Intubation of the NEOnate) multicenter, double-blind, randomized controlled trial included 173 newborn infants requiring nonemergency intubation and compared premedication with atropine and propofol vs atropine, atracurium, and sufentanil[4] (the most frequently used fast-acting, short duration opioid in France[10]). The frequency of prolonged oxygen desaturation did not significantly differ between the 2 groups. The present study reports the results of neurodevelopmental evaluation at 2 years of corrected age from the PRETTINEO trial. Our hypothesis was that propofol was not associated with a higher risk of death or neurodevelopmental delay.

ASQ	Ages and Stages Questionnaire
PRETTINEO	PREmedication Trial for Tracheal Intubation of the NEOnate

Methods

The PRETTINEO multicenter, double-blind, randomized, controlled trial was conducted in 6 French neonatal intensive care units between May 2012 and August 2016. The study protocol has been described previously.[4] This trial included infants hospitalized in a neonatal intensive care unit who required nonemergency intubation. After parental consent was obtained and inclusion criteria fulfilled, infants were randomized and allocated with a 1:1 to receive either a premedication with atropine and propofol or premedication with atropine, atracurium, and sufentanil. All surviving infants enrolled in the trial were eligible for this follow-up evaluation. The ethics committee of Paris Ile de France 3 (reference 2895, July 21, 2011) and the French Medicinal Products Agency (reference A110281-16, May 11, 2011) approved the trial. Parents of all infants signed a written informed consent.

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Interventions

Prior to nasotracheal intubation, infants randomized to the experimental arm received atropine (15 μg/kg) then propofol (2.5 mg/kg for infants weighing >1000 g; 1 mg/kg for infants weighing ≤1000 g). Infants randomized to the control arm received atropine (15 μg/kg), atracurium (0.3 mg/kg), then sufentanil (0.2 μg/kg for infants weighing >1000 g; 0.1 μg/kg for infants weighing ≤1000 g). Treatments were delivered through a double-dummy approach to ensure blinding. In each treatment arm, if adequate anesthesia was not achieved 2 minutes after the last drug injection, supplementary blinded syringes were available to inject a second dose of propofol (1 mg/kg) or atracurium (0.1 mg/kg) according to the randomization group. If anesthesia was still insufficient 2 minutes after the second dose, the operator could choose an open-label drug as rescue therapy and the patient remained in the study.

Outcomes

Principal investigators at each site were responsible for performing follow-up visits and obtaining data at each visit according to local organization (outpatient consultations and/or phone calls) at 2 years of corrected age. Neurodevelopmental outcome was evaluated at 22-26 months of corrected age. Parents completed the Ages and Stages Questionnaire (ASQ), second edition.[11] This questionnaire was validated and previously used in France as a screening tool for psychomotor development for infants with a history of preterm birth.[12,13] The ASQ includes 30 items in 5 neurodevelopmental domains: communication abilities, gross motor skills, fine motor skills, problem solving abilities, and personal-social skills.[11] For each domain, the score obtained by the sum of the items ranges from 0 to 60 and the overall maximum ASQ score is 300 points. For each domain, the score can be categorized using established screening thresholds: an ASQ score <-2 SD below the mean suggests a risk of neurodevelopmental delay in that domain.[13]

Our main outcome was survival without risk of neurodevelopmental delay. Neurodevelopmental delay was defined as no ASQ domain score below threshold at 2 years of corrected age. Other outcomes at 2 years of corrected age included survival, ≥2 ASQ domains below threshold, ≥3 ASQ domains below threshold, mean ASQ score for each domain, and mean total ASQ score.

Statistical Analyses

As in the analysis of the first part of the trial,[4] neurodevelopmental outcomes were analyzed with generalized mixed models adjusted for weight at inclusion (≤1000 g, >1000 g) and treating center as a random effect (exchangeable within center correlation structure).

To handle missing data on ASQ scores, we performed multiple imputation with chained equations using the SAS "MI" procedure.[14,15] Variables included in the imputation model were center, gestational age, birth weight, sex, birth weight <10th percentile for age and sex, 5-minute Apgar score, postmenstrual age at inclusion, weight at inclusion, severe lesions on head ultrasound (intraventricular hemorrhage grade 3 or 4, white matter lesions, or cerebellar lesions) before inclusion and within 7 days after intervention, history of previous intubation, reason for intubation, treatment group, prolonged desaturation after intervention, and hypotension within 1 hour after intervention, defined as a mean arterial blood pressure value (in mm Hg) below gestational age (in weeks). Missing ASQ domains were imputed using predictive mean matching. Overall ASQ score was then estimated using the domain-specific imputed datasets. We generated 30 independent imputed datasets with 20 iterations each. Estimates were pooled according to the Rubin rule. There was no missing data on survival.

The primary analysis was performed on the imputed dataset in the "as treated" study groups. The as-treated atropine-propofol group included all infants who received ≥1 dose of propofol either because they were randomized to the atropine-propofol group or because they received propofol therapy as open-label drug. The as-treated atropine-atracurium-sufentanil group included all infants who were randomized to the atropine-atracurium-sufentanil group who did not receive propofol as open-label therapy. Randomized infants who were not intubated (change in decision) were excluded. This analysis was justified by the concerns raised about potential neurotoxicity of propofol so that the propofol group included all infants having actually received propofol. We also analyzed the main outcome in 3 other sensitivity analyses: the complete as-treated groups without imputation for missing data; the modified intent-to-treat groups (including all infants as randomized except those who were not intubated); and the per protocol groups (including infants who received only premedication as allocated in the randomization process while excluding those who received an open-label drug or who did not receive the allocated premedication). Statistical analyses were conducted using SAS v 9.4 (SAS Institute Inc). All tests were 2-sided, and a P value of <.05 was considered statistically significant.

Results

We randomized 173 infants: 91 in the atropine-propofol group and 82 in the atropine-atracurium-sufentanil group. Five infants were excluded for lack of parental consent or because they were never intubated leaving 87 infants in the atropine-propofol group and 81 in the atropine-atracurium-sufentanil group (modified intention-to-treat groups). For the primary analysis of this study, the "as treated" population included 85 patients who received atropine-propofol either as allocated (n = 83) or open-label (n = 2) and 81 patients treated with atropine-atracurium-sufentanil either as allocated (n = 79) or open-label (n = 2) (**Figure**; available at www.jpeds.com). Baseline and postintervention characteristics of the as treated population are described in **Table I**.

Table I. Baseline and postintervention characteristics in the as-treated population

Characteristics	No. (%)* Atropine-propofol group (n = 85)	Atropine-atracurium-sufentanil group (n = 81)	*P* value†
Baseline characteristics			
Gestational age, wk			
24-26	19 (22.4)	22 (27.2)	.28
27-31	34 (40.0)	39 (48.1)	
32-34	14 (16.5)	6 (7.4)	
35-36	6 (7.1)	7 (8.6)	
≥37	12 (14.1)	7 (8.6)	
Median [IQR]	30 [28; 34]	29 [26; 31]	.12
Boys	45 (52.9)	56 (69.1)	.034
Small for gestational age	15 (17.6)	10 (12.3)	.34
Median postnatal age at inclusion [IQR], d	1 [0; 8]	1 [0; 9]	.57
Weight categories at inclusion, g			
≤1000	26 (30.6)	25 (30.9)	.045
1000-1500	19 (22.4)	31 (38.3)	
>1500	40 (47.1)	25 (30.9)	
5-min Apgar score			
No. (%) with data	84 (99)	81 (100)	
<7	5 (6.0)	13 (16.0)	.039
<5	1 (1.2)	4 (4.9)	
Previous intubation	29 (34.1)	32 (39.5)	.47
Reason for intubation			
Respiratory distress syndrome	57 (67.1)	50 (61.7)	.26
Apnea	3 (3.5)	8 (9.9)	
Surgery	20 (23.5)	15 (18.5)	
Other	5 (5.9)	8 (9.9)	
Head ultrasound before intervention			
No. (%) with data	75 (88.2)	73 (90.1)	
Severe lesion‡	0 (0.0)	4 (5.5)	.26
Postintervention characteristics			
Prolonged desaturation after intervention§	52 (61.2)	53 (65.4)	.57
Hypotension after intervention¶	10 (11.8)	1 (1.2)	.007
Head ultrasound after intervention			
No. (%) with data	83 (97.6)	77 (95.1)	
Severe lesion‡	4 (4.8)	9 (11.7)	.22

*Denominators vary according to the number of missing data for each variable. Percentages may not sum to 100 due to rounding.
†χ^2 test for categorical data and the Wilcoxon rank-sum test for continuous data reporting median values.
‡Intraventricular hemorrhage grade 3 or 4, white matter lesions, or cerebellar lesions.
§SpO_2 (oxygen saturation measured by pulse oximetry) <80% for >60 seconds.
¶Mean arterial blood pressure value (in mm Hg) below gestational age (in weeks).

Outcomes

ASQ questionnaires were collected at 22-26 months of corrected age for 48 out of 81 (59.3%) surviving infants in the atropine-propofol group and 60 out of 74 (81.1%) surviving infants in the atropine-atracurium-sufentanil group. Survival without risk of neurodevelopmental delay at 2 years of corrected age did not differ significantly between the 2 groups in the imputed model: 45 out of 85 (53.7%) patients in the atropine-propofol group and 38 out of 81 (47.3%) patients in the atropine-atracurium-sufentanil group (adjusted risk difference 5.9, 95% CI -10.7 to 22.5, $P = .49$) (Table II). Survival at 2 years of corrected age, number of ASQ domains below threshold, mean total ASQ scores, and mean ASQ scores in each domain did not differ significantly between groups (Table II). Results for the main outcome were consistent in all sensitivity analyses with no significant difference between the 2 groups (Table III; available at www.jpeds.com). Results for all outcomes did not differ significantly between the 2 groups for the complete as-treated case analysis without multiple imputation (Table IV; available at www.jpeds.com).

Discussion

In this planned follow-up study, premedication with atropine-propofol for infants requiring nonemergency intubation was not significantly associated with death or increased risk of neurodevelopmental delay using parent-reported ASQ scores at 2 years of corrected age compared with atropine-atracurium-sufentanil. Using ASQ scores, nearly one-half of survivors were at risk of impaired development, which may seem to be a high proportion. One explanation could be that the ASQ is a screening tool designed to have a high sensitivity and high negative predictive value to identify infants who need more detailed evaluations. In the literature, not all infants with 1 ASQ score below threshold have neurodevelopmental impairments when assessed using other tools such as Bayley Scales of Infant-Toddler Development, Third edition.[16]

Our results do not support significant neurotoxicity of propofol in newborn infants compared with the use of opioids and muscle-blockers. Concerns about potential side effects of propofol are mainly related to the increased risk of systemic hypotension.[7,8] In the first part of the trial, hypotension occurred in 13.3% of infants in the atropine-propofol group and 2 required an intervention (volume expansion or dopamine).[4] Other studies reported 40%-75% of patients experiencing hypotension following propofol premedication with various definitions of hypotension.[7,8] However, to date, there is no evidence that propofol-induced hypotension results in decreased cerebral oxygenation and, thus, cerebral lesions.[5]

Animal and cellular models suggested potential developmental neurotoxicity of propofol (such as increased cell death, dysregulation of neurogenesis or decreases in neurotrophic factor expression).[9] Extrapolation of these models to humans is very challenging and highly limited by the impact of other clinical conditions, such as nutrition, oxygenation, and simultaneous noxious stimuli, which cannot be controlled easily in the experimental setting. Studies indicate that early painful experiences impair neurodevelopment in infants born prematurely, causing long-term alterations in nociception.[17] Hence, premedication for nonemergency neonatal intubations is strongly recommended. The remaining question is which drug(s) to use. To date and in our opinion, there is no clear data indicating that any regimen is safer than another. Our study is reassuring for neurodevelopmental outcome at 2 years of corrected age using propofol compared with the combination of a fast-acting opioid and a

Table II. Results for outcomes in the as-treated population with multiple imputation analysis

	No of events*/No in group (%)		Adjusted risk differences: Atropine-propofol group minus Atropine-atracurium-sufentanil (95% CI)†	*P* value†
	Atropine-propofol group (n = 85)	Atropine-atracurium-sufentanil group (n = 81)		
Number of survivors with imputed ASQ scores	33 (40.7)	14 (18.9)		
Main outcomes				
Survival without risk of neurodevelopmental delay at 2 y of corrected age‡	45 (53.7)	38 (47.3)	5.9 (−10.7; 22.5)	.49
Other outcomes				
Survival at 2 y of corrected age	81 (95.3)	74 (91.4)	2.7 (−4.2; 9.7)	.44
Survivors at 2 y of corrected age	n=81	n=74		
≥1 ASQ domain below threshold at 2 y of corrected age‡	35 (43.7)	35 (48.2)	−4.8 (−22.1; 12.6)	.59
≥2 ASQ domains below threshold at 2 y of corrected age‡	19 (24.4)	17 (24.1)	−0.9 (−15.7; 13.9)	.90
≥3 ASQ domains below threshold at 2 y of corrected age‡	11 (14.0)	8 (11.5)	−0.2 (−11.2; 10.7)	.97
Communication score below threshold	23 (28.9)	16 (22.1)	2.6 (−12.4; 12.5)	.74
Gross motor score below threshold	17 (21.7)	16 (22.1)	−2.1 (−16.9; 12.7)	.78
Fine motor score below threshold	10 (12.5)	11 (16.1)	−3.9 (−16.0; 8.1)	.52
Problem solving score below threshold	8 (10.0)	11 (16.1)	−7.3 (−18.7; 4.1)	.21
Personal social score below threshold	15 (18.7)	12 (16.9)	1.4 (−11.8; 14.7)	.83
Total ASQ score, mean (SD)	219.9 (56.4)	219.1 (59.5)	1.2 (−18.4; 20.7)	.91
Communication score, mean (SD)	40.3 (18.5)	42.8 (16.9)	−2.4 (−8.6; 3.8)	.45
Gross motor score, mean (SD)	45.8 (18.0)	45.8 (17.2)	0.1 (−6.0; 6.2)	.97
Fine motor score, mean (SD)	47.9 (10.9)	47.2 (12.7)	0.7 (−3.4; 4.8)	.75
Problem solving score, mean (SD)	41.8 (12.8)	41.0 (13.5)	0.9 (−3.6; 5.4)	.69
Personal social score, mean (SD)	44.1 (13.2)	42.2 (13.8)	1.9 (−2.8; 6.5)	.43

*Average number of events from the imputed dataset.
†Generalized linear mixed-effects models adjusted for weight at inclusion (≤1000 g,>1000 g) taking into account within-center correlation.
‡For each domain, a score > 2 SDs below the mean, using established screening cut-off points (Squire, 2009) was reported. If a score was below threshold in at least one domain, the global ASQ score was considered below threshold.

muscle blocker. However, longer follow-up through school age is necessary to confirm these conclusions.

This study has several limitations. First, our study could be underpowered due to the small number of patients and because the sample size calculation was not based on the 2-year outcomes. Obtaining parental consent before intubation was challenging, and the trial was prematurely interrupted for logistic reasons.[4] However, the results were consistent for all outcomes and in the sensitivity analyses. Second, we had to impute nearly one-third of ASQ scores with more imputation in the atropine-propofol group (40.7% vs 18.9%). Among survivors, ASQ scores were available in the appropriate range of ages for 108 out of 155 (69.7%) patients. The 22-26 months range of ages could introduce a bias between patients evaluated at an early vs later age, but there was no significant difference in age at evaluation between the 2 groups. Third, we did not have any data on parental socioeconomic status, which would have been important to include in the imputation model because of its potential impact on neurodevelopmental outcome. However, we included all baseline characteristics available in the multiple imputation model and we conducted a sensitivity analysis on complete cases without multiple imputation. This analysis showed consistent results. Fourth, we could not specifically assess the effect of propofol-induced hypotension because of the low frequency of this event. Even if hypotension was more frequent in the atropine-propofol group, it was apparently not associated with an increased risk of neurodevelopmental delay at 2 years of corrected age. Fifth, an imbalance in baseline characteristics (sex and weight) between groups might have caused a bias.

In summary, premedication for nonemergency neonatal intubation with atropine-propofol was not significantly associated with death or parent-reported risk of neurodevelopmental delay using ASQ at 2 years of corrected age compared with atropine-atracurium-sufentanil. Further studies on larger cohorts should focus on long-term tolerance and safety of propofol to support our results. ■

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Appendix

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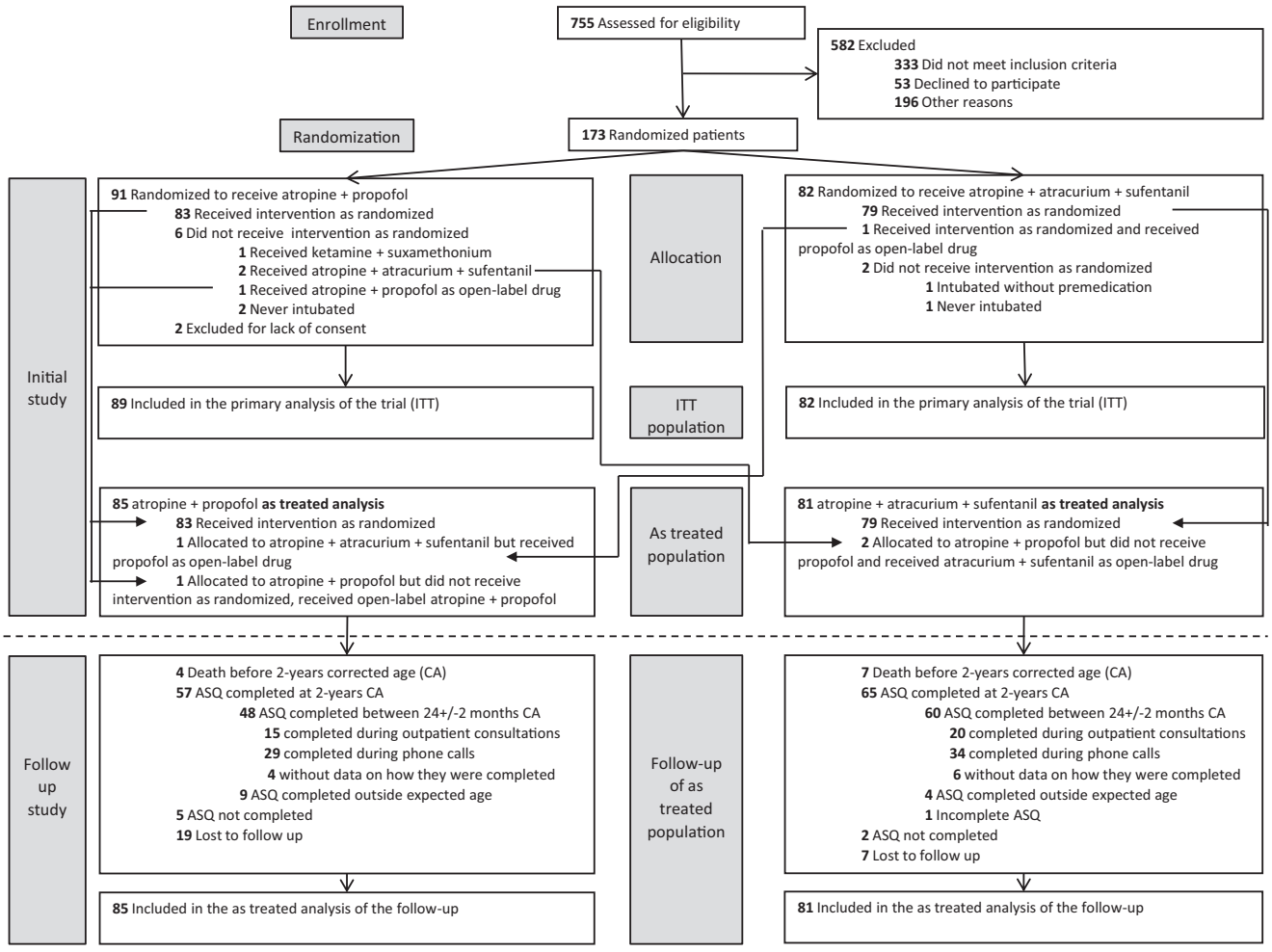

Figure. Population flow chart. Five patients from the ITT analysis were excluded from the as treated population: one because he/she received ketamine and suxamethonium as open-label drugs, the second because he/she was intubated without premedication and three patients because they were never intubated. *ITT*, intent-to-treat.

Table III. Sensitivity analysis for survival without risk of neurodevelopmental delay at 2 years of corrected age (main outcome)

	No of events*/No in group (%)		Adjusted risk differences: Atropine+propofol group minus Atropine + atracurium + sufentanil (95% CI)†	*P* value†
	Atropine + propofol group	Atropine + atracurium + sufentanil group		
As treated population, multiple imputation analysis (primary analysis)	45/85 (53.7)	38/81 (47.3)	5.9 (−10.7; 22.5)	.49
As treated population, complete cases analysis	31/52 (59.6)	30/67 (44.8)	14.2 (−3.4; 31.8)	.11
Modified-ITT population, multiple imputation analysis	46/87 (53.3)	38/81 (47.6)	5.5 (−11.0; 22.0)	.51
Per protocol population, multiple imputation analysis	36/67 (54.1)	37/78 (47.5)	5.5 (−12.3; 23.3)	.54

ITT, intent-to-treat.
*Average number of events from the imputed dataset.
†Generalized linear mixed-effects models adjusted for weight at inclusion (≤1000 g, >1000 g) taking into account within-center correlation.

Table IV. Results for outcomes in the complete case population

	No of events/No in group (%)		Adjusted risk differences: Atropine-propofol group minus Atropine-atracurium-sufentanil (95% CI)*	*P* value†
	Atropine-propofol group (n = 85)	Atropine-atracurium- sufentanil group (n = 81)		
Main outcomes				
Survival without risk of neurodevelopmental delay at 2 y of corrected age*	31/52 (59.6)	30/67 (44.8)	14.2 (−3.4; 31.8)	.11
Other outcomes				
Survival at 2 y of corrected age	81/85 (95.3)	74/81 (91.4)	2.7 (−4.2; 9.7)	.44
Survivors at 2 y of corrected age,				
At least 1 ASQ domain below threshold at 2 y of corrected age‡	17/48 (35.4)	30/60 (50.0)	−14.9 (−33.2; 3.4)	.11
At least 2 ASQ domains below threshold at 2 y of corrected age‡	10/48 (20.8)	16/60 (26.7)	−7.1 (−22.1; 8.0)	.35
At least 3 ASQ domains below threshold at 2 y of corrected age‡	7/48 (14.6)	8/60 (13.3)	−2.2 (−15.0; 10.6)	.74
Communication score below threshold	13/48 (27.1)	14/61 (23.0)	−0.6 (−16.3; 15.0)	.94
Gross motor score below threshold	8/48 (16.7)	15/60 (25.0)	−9.8 (−24.1; 4.5)	.18
Fine motor score below threshold	6/48 (12.5)	10/61 (16.4)	−4.5 (−17.7; 8.8)	.51
Problem solving score below threshold	4/48 (8.3)	11/61 (18.0)	−11.5 (−23.7; 0.7)	.064
Personal social score below threshold	9/48 (18.8)	11/61 (18.0)	0.2 (−14.3; 14.8)	.98
Number of survivors with total ASQ score available	48 (59.3)	60 (81.1)		
Total ASQ score, mean (SD)	224.4 (59.9)	215.8 (63.7)	8.4 (−15.5; 32.3)	.49
Communication score, mean (SD)	41.4 (18.5)	42.4 (17.2)	−1.1 (−7.8; 5.6)	.74
Gross motor score, mean (SD)	48.2 (16.2)	44.3 (18.1)	4.0 (−2.5; 10.6)	.22
Fine motor score, mean (SD)	47.5 (10.7)	47.3 (13.0)	0.2 (−4.4; 4.9)	.92
Problem solving score, mean (SD)	42.3 (13.0)	40.2 (13.9)	2.1 (−3.1; 7.3)	.42
Personal social score, mean (SD)	45.0 (13.2)	41.5 (14.3)	3.4 (−1.9; 8.8)	.20

*For each domain, a score lower than 2 SDs from the mean, using established screening cut-off points (Squire, 2009) was reported. If a score was below threshold in at least 1 domain, the global ASQ score was considered below threshold.
†Generalized linear mixed-effects models adjusted for weight at inclusion (≤1000 g,>1000 g) taking into account within-center correlation.
‡For each domain, a score > 2 SDs below the mean, using established screening cut-off points (Squire, 2009) was reported. If a score was below threshold in at least one domain, the global ASQ score was considered below threshold.