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Association Between a Single General Anesthesia Exposure Before Age 36 Months and Neurocognitive Outcomes in Later Childhood

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Abstract

IMPORTANCE—Exposure of young animals to commonly used anesthetics causes neurotoxicity including impaired neurocognitive function and abnormal behavior. The potential neurocognitive and behavioral effects of anesthesia exposure in young children are thus important to understand.

OBJECTIVE—To examine if a single anesthesia exposure in otherwise healthy young children was associated with impaired neurocognitive development and abnormal behavior in later childhood.

DESIGN, SETTING, AND PARTICIPANTS—Sibling-matched cohort study conducted between May 2009 and April 2015 at 4 university-based US pediatric tertiary care hospitals. The study cohort included sibling pairs within 36 months in age and currently 8 to 15 years old. The exposed siblings were healthy at surgery/anesthesia. Neurocognitive and behavior outcomes were prospectively assessed with retrospectively documented anesthesia exposure data.

EXPOSURES—A single exposure to general anesthesia during inguinal hernia surgery in the exposed sibling and no anesthesia exposure in the unexposed sibling, before age 36 months.

MAIN OUTCOMES AND MEASURES—The primary outcome was global cognitive function (IQ). Secondary outcomes included domain-specific neurocognitive functions and behavior. A detailed neuropsychological battery assessed IQ and domain-specific neurocognitive functions. Parents completed validated, standardized reports of behavior.

RESULTS—Among the 105 sibling pairs, the exposed siblings (mean age, 17.3 months at surgery/anesthesia; 9.5% female) and the unexposed siblings (44% female) had IQ testing at mean ages of 10.6 and 10.9 years, respectively. All exposed children received inhaled anesthetic agents, and anesthesia duration ranged from 20 to 240 minutes, with a median duration of 80 minutes. Mean IQ scores between exposed siblings (scores: full scale = 111; performance = 108; verbal = 111) and unexposed siblings (scores: full scale = 111; performance = 107; verbal = 111) were not statistically significantly different. Differences in mean IQ scores between sibling pairs were: full scale = −0.2 (95% CI, −2.6 to 2.9); performance = 0.5 (95% CI, −2.7 to 3.7); and verbal = −0.5 (95% CI, −3.2 to 2.2). No statistically significant differences in mean scores were found between sibling pairs in memory/learning, motor/processing speed, visuospatial function, attention, executive function, language, or behavior.

CONCLUSIONS AND RELEVANCE—Among healthy children with a single anesthesia exposure before age 36 months, compared with healthy siblings with no anesthesia exposure, there were no statistically significant differences in IQ scores in later childhood. Further study of repeated exposure, prolonged exposure, and vulnerable subgroups is needed.

According to the 2010 US Census, there are approximately 20 million children in the United States younger than 5 years, of whom about 10% undergo general anesthesia/deep sedation each year.[1–3] Any potential neurocognitive risks of pediatric anesthesia are a major scientific and public health issue.

In both rodents and nonhuman primates, exposure of developing brains to commonly used anesthetic agents produces neurotoxicity, impairing learning, memory, attention, motor function, and behavior in adult life.[4,5] However, it remains unclear if these findings are applicable to children and if pediatric anesthesia might have negative neurodevelopmental effects.

Epidemiological studies have found an association of impaired neurodevelopment with even a single anesthesia exposure.[6,7] However, other clinical studies have reported an association only with multiple episodes of exposure,[8] and still others have not found any association.[9] Thus, clinical studies to date have not fully answered the important question of whether a single anesthesia exposure may pose neurodevelopmental risks that become evident later in life.

Otherwise healthy young children undergoing elective surgery make up a very large proportion of children receiving general anesthesia. If exposures to general anesthesia pose long-term neurodevelopmental risks in healthy children, then there is a need to assess the neurodevelopmental risks of childhood anesthesia exposure.[10,11] A consensus statement released in October 2015, endorsed by 19 different professional organizations,[12] advocated for more research to evaluate the neurodevelopmental effects of anesthesia exposure in early childhood.

The Pediatric Anesthesia Neurodevelopment Assessment (PANDA) study used a sibling-matched cohort design to test the hypothesis that a single exposure to general anesthesia in healthy children younger than 3 years was associated with, at ages 8 to 15 years, an

increased risk of impaired global cognitive function (IQ) as the primary outcome and abnormal domain-specific neurocognitive functions and behavior as secondary outcomes.

Methods

Using a sibling-matched cohort design, neuropsychological functions and behavior were assessed in children aged 8 to 15 years. The study inclusion criteria were (1) exposed: children who had a single general anesthetic before age 36 months for elective inguinal hernia surgery during 2000–2010; American Society of Anesthesiologists (ASA) Physical Status 1, defined as children who are healthy, or ASA Physical Status 2, defined as children with very limited systemic diseases with no functional limitations; 36 weeks' gestational age or older at birth and (2) unexposed: biologically related siblings (half or full) closest in age (within 3 years) to the exposed child, with no anesthesia exposure before age 36 months and 36 weeks' gestational age or older at birth.

The sibling-matched comparison group was chosen to minimize effects of genetic background, familial environment, parental education, and other indexes of socioeconomic status, all key factors affecting neurodevelopment.[13,14] An age range of 0 to 36 months was chosen as the exposure age range because this period encompasses peak synaptogenesis of various human brain regions.[15,16]

The study's prespecified primary outcome was global cognitive function (IQ); secondary outcomes were domain-specific cognitive functions and behavior. Selection of outcomes was based on one of the following criteria:

- Specific neurocognitive domains with deficits identified in animal studies (memory, attention, and motor function)[4,17,18]
- Neurocognitive domains with demonstrated impairments in human studies (language)[8,19]
- Other human functions considered to be important in daily living or school/work performance (executive function and attention)

Assessment at ages 8 to 15 years was chosen because neuropsychological testing of all domains was both reliable and valid at these ages and it allowed enough follow-up time for impairments to emerge.

A 2-day meeting was held in Baltimore, Maryland, in June 2010 with neuropsychology and neurodevelopment experts from 6 institutions to develop the PANDA neuropsychological battery (eTable 1 in the Supplement).

Following approval by the institutional review board at each institution that participated as a study site (Columbia University Medical Center [CUMC], New York, New York; Children's Hospital of Philadelphia [CHOP], Philadelphia, Pennsylvania; Boston Children's Hospital [BCH], Boston, Massachusetts; and Monroe Carell Jr Children's Hospital at Vanderbilt [VCH], Nashville, Tennessee), participants were screened and recruited between May 2009 and April 2015 (Figure).

After obtaining written informed consent from parents and assent from children, we randomly assigned sibling pairs to individually undergo a single testing session using the PANDA neuropsychological battery. All testers were trained by a pediatric neuropsychologist and blinded to the exposure status of the siblings. Accompanying parents completed standardized questionnaires on behavior and were interviewed regarding medical, social, and family history. Race/ethnicity data were included to document race/ethnicity composition of the study cohort and to evaluate that it is representative of the US population. Race/ethnicity data were reported by parents using predetermined fixed categories. Clinical data (surgical procedure, all anesthetic agents and perioperative medications, and documented perioperative complications) were abstracted from anesthesia and medical records at each study site. Total anesthesia duration was defined as the time between initial administration of anesthesia and the documented end of record for anesthesia. Each site was responsible for entering all data into a study-specific electronic data capture system. Ten percent of neuropsychological testing data were rescored and reviewed for accuracy and completeness with less than 1% error found. Three pediatric anesthesiologists reviewed clinical records for consistency and accuracy. All data entry was checked by trained research personnel at the coordinating site, and any error (<2%) was rechecked and corrected.

For analysis of the primary outcome, data were included only if both siblings within each pair had complete data. Secondary outcomes were analyzed in those sibling pairs only with complete data for both the primary outcome and the specific secondary outcome.

Sample size was estimated to detect an IQ difference of 4.5 between sibling pairs at $\alpha = .05$ and 80% power based on 2-sided paired *t* tests. The selection of an IQ difference of 4.5 was based on a pilot study conducted in 28 sibling pairs (none of the data from the pilot study were included in the present study).[20] An IQ difference of 4.5 (or 0.3 SD) would recenter the population mean to result in a significant population effect on neurodevelopment of children.[21,22] The final sample size for the study (113 sibling pairs) included a 25% increase of the calculated sample size of 90 sibling pairs to account for between-sibling correlation and multivariable adjustments.

The initial analysis was performed in the combined cohort of both exposed and unexposed siblings using mixed-model analysis of variance (ANOVA). It considered dependence between siblings within a pair and evaluated if any of the prespecified variables (eTable 2 in the Supplement) were significantly associated with the primary outcome or with any of the secondary outcomes.

A 2-tailed paired *t* test was first used to analyze the primary and secondary outcomes. In outcomes found to be significant ($P < .05$), further analysis using a linear mixed-effects model that considered dependence between siblings within a pair was then performed to examine the association between exposure and outcome, with adjustment for variables that were significant ($P < .05$) in the mixed ANOVA and unshared by the siblings. For outcomes found to be significant by paired *t* test and that had known clinical cutoffs, a McNemar test for matched pairs was performed in dichotomized outcomes, followed by mixed-effects logistic regression adjusting for all significant covariates. The primary outcome and

secondary outcomes were also analyzed in the same-sex sibling pairs and in sibling pairs with no further anesthesia exposure.

To examine association of age and duration of exposure with the primary outcome, ANOVA was performed between IQ difference and the 3 different ages of exposure (0–11 months, 12–23 months, and 24–36 months) as well as between IQ difference and exposure durations at 60-minute intervals. Exposures of shorter than 60 minutes were previously found to have no effect on neurocognitive outcome[23] and exposures of 120 minutes or more were associated with an increased risk of learning disability.[8]

All analyses were performed using R software.[24] All demographic, neurocognitive outcome, and behavior scores are presented as means with standard deviations. Differences in neurocognitive outcome and behavior scores between siblings are presented as change scores with 95% confidence intervals. All tests for statistical significance were 2-tailed and $P < .05$ was deemed significant.

Results

A total of 216 sibling pairs were eligible based on exclusion/inclusion criteria; of these, 130 sibling pairs were successfully recruited and 116 sibling pairs (BCH, n=50; CHOP, n=23; CUMC, n=20; and VCH, n=23) were tested at the 4 study sites (Figure). A total of 105 sibling pairs were included in primary outcome analysis and between 97 and 105 pairs were included in the analysis of secondary outcomes (eTables 3A and 3B in the Supplement).

Of the 105 sibling pairs, the mean age at testing was 10.6 (SD, 2.0) years for exposed children and 10.9 (SD, 1.7) years for unexposed children (Table 1). There were 104 full-sibling pairs and one half-sibling pair. Exposed siblings were 90% male and only 56% of unexposed siblings were male. There were 42 same-sex sibling pairs; 39 of these pairs were male-male. More than 80% of the exposed cohort was deemed to be ASA Physical Status 1 at the time of surgery. Forty-four exposed siblings were older siblings and 61 were younger siblings (Table 1). Family socioeconomic data were collected by parental report and are described in Table 2.

All exposed children received inhaled anesthetic agents (43 sevoflurane; 5 isoflurane; 57 sevoflurane and isoflurane). Twenty-eight children received both inhaled and intravenous agents (propofol, thiopental, ketamine, and midazolam), 75 children received opioids, and 39 received adjunct caudal anesthesia. Thirty-three children received midazolam for premedication. The mean duration of anesthesia was 84 (SD, 33) minutes and ranged from 20 to 240 minutes, with a median duration of 80 minutes. Sixty-four children (61%) had an anesthesia duration between 60 and 119 minutes. Anesthesia after 36 months occurred in 18 exposed and 23 unexposed siblings. Differences of IQ scores were comparable between the entire cohort and the cohort of 67 exposed and unexposed sibling pairs who had a single lifetime anesthetic and no lifetime anesthetic, respectively (eTable 4 in the Supplement).

In mixed ANOVA analysis of the combined cohort, significant variables associated with IQ scores included race, study site, and indexes of socioeconomic status, while sex was a

significant variable associated with several secondary outcomes (eTable 2 in the Supplement).

Mean IQ scores were not statistically significantly different between the exposed cohort (full-scale IQ = 111 [95% CI, 108–113]; performance IQ = 108 [95% CI, 105–111]; verbal IQ = 111 [95% CI, 108–114]) and unexposed siblings (full-scale IQ = 111 [95% CI, 108–113]; performance IQ = 107 [95% CI, 105–110]; verbal IQ = 111 [95% CI, 109–114]). Differences in mean IQ scores between exposed and unexposed siblings were, for full-scale IQ, 0.2 (95% CI, −2.6 to 2.9), performance IQ, 0.5 (95% CI, −2.7 to 3.7), and verbal IQ, −0.5 (95% CI, −3.2 to 2.2) (Table 3). Between siblings, there were no statistically significant differences at the 3 age ranges of exposure in full IQ score (differences at 0–11 months, 1 [95% CI, −4.1 to 6.1]; at 12–23 months, 1 [95% CI, −3.4 to 5.4]; and at 24–36 months, −1 [95% CI, −5.8 to 3.8]) or at various durations of exposures in full IQ score (differences for 0–59 minutes of exposure, 2 [95% CI, −4 to 8]; for 60–119 minutes, 0 [95% CI, −3.4 to 3.4]; and for ≥120 minutes, −2 [95% CI, −8.2 to 4.2]) (Table 4). There were no statistically significant differences in verbal IQ or performance IQ change scores at the 3 ages of exposure or at various durations of exposure (Table 4). Mean IQ scores were not statistically significantly different in the 42 same-sex exposed siblings (full-scale IQ = 109 [95% CI, 105–113]; performance IQ = 107 [95% CI, 103–111]; verbal IQ = 111 [95% CI, 108–114]) and unexposed siblings (full-scale IQ = 110 [95% CI, 105–115]; performance IQ = 108 [95% CI, 103–113]; verbal IQ = 110 [95% CI, 105–115]) (eTable 5A in the Supplement) and in the subset of 67 sibling pairs with no subsequent anesthesia exposures (eTable 4 in the Supplement).

Among the secondary outcomes, paired *t* tests showed statistically significantly different mean scores between siblings for verbal fluency (difference, −1; 95% CI, −1.7 to −0.3)[25]; behavior (Child Behavior Checklist [CBCL]) (internalizing: difference, 3.2 [95% CI, 1.1–5.3]; externalizing: difference, 2.1 [95% CI, 0–4.2], and total problems: difference, 2.7 [95% CI, 0.6–4.7])[26]; and adaptive behavior (Adaptive Behavior Assessment System, Second Edition [ABAS-II]) (social composite: difference, −3.3; 95% CI, −6.1 to −0.6)[27] (Table 3). Sex was the only significant covariate associated with verbal fluency, CBCL, and ABAS-II scores in the combined cohort. Differences in mean verbal fluency, CBCL, and ABAS-II scores were not statistically significant after adjusting for sex and in same-sex sibling pairs (verbal fluency, −0.6 [95% CI, −1.7 to 0.5]; CBCL internalizing, −0.1 [95% CI, −3.1 to 2.8]; CBCL externalizing, 0.9 [95% CI, −2.4 to 4.2]; CBCL total problems, −0.8 [95% CI, −3.8 to 2.2]; and ABAS-II social composite, −0.9 [95% CI, −3.9 to 2.2]) (eTable 5A in the Supplement). No statistically significant differences between siblings were found in all remaining secondary outcomes including domain-specific neurocognitive functions of memory, learning, motor or processing speed, visuospatial function, attention, language, executive function, and other areas of adaptive behavior (Table 3).

Categorical analysis using clinical cutoffs was performed for CBCL and ABAS-II scores (eTable 2 in the Supplement). There were 21 (21%) exposed and 10 (10%) unexposed siblings with abnormal CBCL internalizing scores (>60). This was statistically significant even after adjusting for sex (eTable 2 in the Supplement). The limited number of same-sex siblings precluded further subgroup analyses (eTable 5B in the Supplement).

Discussion

Results of the PANDA study indicate that there was no statistically significant difference in full-scale IQ score between siblings with and without a single anesthesia exposure before age 3 years, with a mean difference of 0.2 IQ points. The exposed siblings could score between 2.9 IQ points higher or 2.6 IQ points lower compared with unexposed siblings based on the 95% confidence interval. At an individual level, differences of 2.6 to 2.9 IQ points between 2 healthy children are within the reliability of measurement for IQ testing[28] and are clinically undetectable. In population studies of lead exposure, mean IQ losses of 6 points have been reported,[21] much more than the mean difference of 0.2 IQ points in the present study. The societal significance of a possible negative shift of the population IQ mean by 2.6 points remains uncertain because it depends on how many children may be at risk.[22]

There were no statistically significant differences between exposed and unexposed siblings in secondary outcomes using mean scores of memory, attention, visuospatial function, executive function, language, motor and processing speed, or behavior.

Differences in mean behavior scores between exposed and unexposed siblings became statistically nonsignificant after adjustment for sex. However, even after adjustment for sex, more exposed children had clinically abnormal internalizing behavior scores than unexposed siblings. With the limited number of exposed girls and same-sex female sibling pairs, further analysis to examine the apparent sex-exposure interaction in behavior was not possible.

Previous clinical studies examining associations between early-life anesthesia exposure and neurodevelopmental outcomes were limited by the lack of clinical details of anesthesia exposure and an inability to adjust for confounders, such as socioeconomic status and genetic influences.[8,29–32] Children included in these earlier studies were also exposed to anesthesia at a wide range of ages, ranging from the first 12 months of life up to 4 years.[8,29,30] Outcomes included academic performance, clinical diagnoses of learning disability, attention-deficit/hyperactivity disorder, developmental disabilities, IQ, and more detailed scores derived from neuropsychological testing.[6,7,9,29,30,32,33]

The recent interim analysis of the General Anaesthesia and Awake–Regional Anaesthesia (GAS) trial found that cognitive, language, and motor functions at age 2 years were comparable between children exposed to general sevoflurane anesthesia and regional anesthesia.[23] However, the GAS trial's prespecified primary outcome of global cognitive function at age 5 years is still pending. Longitudinal neurodevelopmental outcome studies have documented that follow-up is important to obtain accurate estimates of neurodevelopmental morbidities.[34,35] The assessment of the PANDA study was made at ages 8 to 15 years, allowing time for any neurocognitive impairment to become evident.

Socioeconomic status in the present study was significantly associated with IQ in the combined exposed and unexposed cohort, consistent with the established important role of socioeconomic status in neurodevelopment.[13,14,36] These findings further validated the use of a sibling-matched cohort study design.

Sibling comparison also minimized influences of genetic background. Monozygotic twin studies of anesthesia exposure and school performance suggested that lower scores may reflect genetic vulnerabilities associated with the need for anesthesia rather than an effect of anesthesia exposure per se.[37] The findings of this study do not preclude the possibility that there may be genetically vulnerable subgroups of children.

The present study examined exposures during inguinal hernia repair surgery only. In contrast, outcomes in most existing studies were assessed in various surgical and nonsurgical procedures.[7,8,30,31] Differences between the results of the present study and those of others may be due to confounding by indications for anesthesia/surgery.

There was no evidence that duration of anesthesia exposure of 120 minutes or longer was associated with larger differences in IQ between siblings. There were also no apparent differences in IQ comparing anesthesia exposure during the first, second, or third year of life. However, in both cases, the number of children in each subgroup was small; therefore, the absence of IQ differences across various durations or at different ages requires further confirmation.

This study has several limitations. First, the present results do not provide data regarding the neurocognitive risks of repeated episodes of anesthesia exposure, more prolonged durations of exposures, or in specific vulnerable subgroups of children, such as premature infants and those with serious comorbidities. These results suggest that future clinical research to assess the neurodevelopmental effects of anesthesia exposure should be directed toward examining behavioral outcomes and identifying possible vulnerable subgroups, including exposure effects in girls.

Second, durations of anesthesia were used to quantitatively estimate exposure because durations could be reasonably ascertained while exposure to specific anesthetic agents could not. A detailed review of all medical records was performed to assess the occurrence of significant perioperative adverse events because they may influence long-term neurocognitive outcome. However, more than 50% of the intraoperative records were paper records; thus, the data may not be complete. Given the lack of differences associated with anesthesia exposure, this limitation was unlikely to affect the results of the study.

Third, recruitment bias may have been introduced because the surgical procedures in the exposed cohort occurred years ago. The sibling cohort had much higher IQs than the population mean, reflecting a possible recruitment bias for children with higher socioeconomic status. However, the sibling-matched cohort design likely minimized the effects of bias. Bias may also be present because of lack of blinding to exposure status in behavioral outcomes, which were derived from parental reports.

Fourth, the sex imbalance of the exposed cohort may limit the generalizability of the results for female children. The exposed cohort consisted of 95 male and only 10 female children. Most common elective procedures during the first 36 months of life—including inguinal herniorrhaphy, hypospadias repair, circumcision, and pyloromyotomy—are predominantly or exclusively performed in male children. Therefore, arguably the unbalanced sex

distribution reflected the clinical population at potential risk. Nevertheless, additional studies are needed among girls to explore the possibility of an exposure and sex interaction.

Fifth, 23 unexposed siblings had anesthesia after age 3 years. However, the true neurodevelopmental effects are unlikely to be observed because the results were comparable in the entire cohort and in the 67 sibling pairs who had no subsequent anesthesia.

Conclusion

Among healthy children with a single anesthesia exposure before age 36 months, compared with healthy siblings with no anesthesia exposure, there were no statistically significant differences in IQ scores in later childhood. Further study of repeated exposure, prolonged exposure, and vulnerable subgroups is needed.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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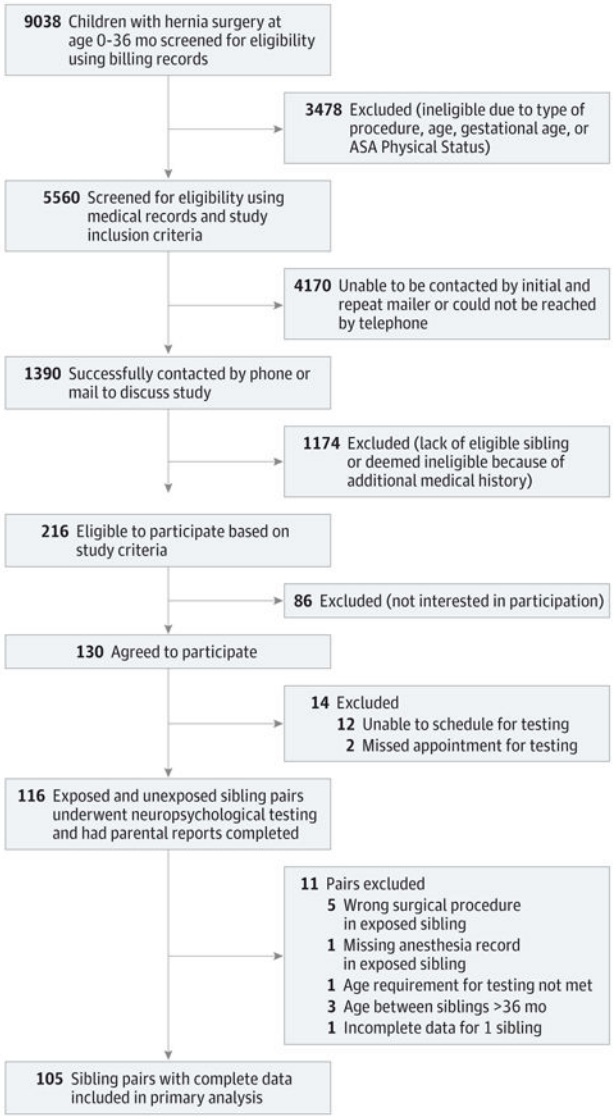

Figure. Participant Flow in the Pediatric Anesthesia Neurodevelopment Assessment Study
ASA indicates American Society of Anesthesiologists.

Table 1

Demographics of Participant Sibling Pairs Exposed and Unexposed to Anesthesia at Age 0 to 36 Months

Characteristics	Exposed (n = 105)	Unexposed (n = 105)
Age at anesthesia exposure, mean (SD), mo	17.3 (10.9)	
0–11 (n = 33)	3.7 (2.4)	
12–23 (n = 39)	17.1 (3.0)	
24–36 (n = 33)	30.5 (3.8)	
Duration of anesthesia, mean (SD) [range], min		
All exposed	84 (33) [20–240]	
0–59 (n = 24)	47 (11)	
60–119 (n = 64)	84 (18)	
≥120 (n = 17)	138 (29)	
Age at testing, mean (SD), y	10.6 (2.0)	10.9 (1.7)
ASA Physical Status at surgery, No. (%)[a]		
1	85 (81)	
2	20 (19)	
Sex, No. (%)		
Male	95 (90)	59 (56)
Female	10 (10)	46 (44)
Birth order, No. (%)		
Older sibling	44 (42)	61 (58)
Younger sibling	61 (58)	44 (42)
Size (based on weight) for gestational age, No. (%)		
Small	10 (9.5)	6 (6)
Appropriate	84 (80)	89 (85)
Large	11 (10)	10 (9.5)
Race, No. (%)		
White	90 (86)	90 (86)
Nonwhite	14 (13)	14 (13)
Missing	1 (1)	1 (1)
Ethnicity, No. (%)		
Hispanic	4 (4)	4 (4)
Non-Hispanic	98 (93)	98 (93)
Missing	3 (3)	3 (3)
Anesthesia or surgery after 36 mo, No. (%)	18 (17)	23 (22)
Enrolled in special education program, No. (%)	16 (15)	14 (13)

[a] American Society of Anesthesiologists (ASA) Physical Status class 1: healthy patients; class 2: patients with very mild systemic disease with no functional limitations.

Table 2

Socioeconomic Characteristics of the Study Participants' Parents

Characteristics	Maternal, No. (%) (n = 105)	Paternal, No. (%) (n = 105)
Income, $		
Unemployed	13 (12)	1 (1)
≤40 000	36 (34)	13 (12)
40 001–80 000	22 (21)	27 (26)
80 001–100 000	22 (21)	42 (40)
>100 000	8 (8)	16 (15)
Missing	4 (4)	6 (6)
Education		
≤12th grade	18 (17)	24 (23)
2 years of college	13 (12)	12 (11)
4 years of college	32 (30)	32 (30)
Postgraduate	42 (40)	34 (32)
Missing	0	3 (3)
Housing		
Own	91 (87)	88 (84)
Rent	14 (13)	11 (10)
Other	0	2 (2)
Missing	0	4 (4)
Marital status		
Single	5 (5)	5 (5)
Married	94 (90)	96 (91)
Divorced	4 (4)	1 (1)
Other	2 (2)	2 (2)
Missing	0	1 (1)
Insurance		
No insurance	2 (2)	2 (2)
Medicaid	7 (7)	2 (2)
Other insurance	96 (91)	97 (92)
Missing	0	4 (4)

Table 3

Summary of Results of Neuropsychological Testing and Parental Reports[a,b]

Domains	Neurocognitive Outcomes	Specific Tests	Specific Scores	Score Range	Assessment Instruments	No. of Sibling Pairs	Mean (95% CI)		
							Exposed	Unexposed	Difference, Exposed – Unexposed
Global cognitive function	Global cognitive function	Full-scale IQ	Composite score	40–160	WASI	105	111 (108–113)	111(108–113)	0.2 (−2.6 to 2.9)
		Performance IQ				105	108 (105–111)	107 (105–110)	0.5 (−2.7 to 3.7)
		Verbal IQ				105	111 (108–114)	111 (109–114)	−0.5 (−3.2 to 2.2)
Memory and learning	Visual memory	Memory for faces	Scaled score	1–19	NEPSY-II	104	10 (9.4–10.6)	11 (10.6–11.4)	−0.5 (−1.1 to 0.1)
		Delayed memory for faces				103	11 (10.4–11.6)	11 (10.4–11.6)	−0.4 (−1.2 to 0.4)
	Verbal memory	Total trials 1–5	T score	20–80	CVLT-C	103	52 (50–54.1)	54 (52–55.9)	−1.6 (−4.1 to 0.9)
Motor speed and processing speed	Motor speed	Dominant hand time	Time(s)		Grooved pegboard	102	71 (67–75)	70 (66–74)	1.4 (−3.5 to 6.3)
		Nondominant hand time				104	80 (75–85)	80 (75–85)	−0.3 (−6.9 to 6.4)
	Processing speed	Coding	Scaled score	1–19	WISC-IV	103	9 (8.4–9.6)	10 (9.4–10.6)	−0.4 (−1.1 to 0.2)
Visuospatial	Visuospatial	Block design	T score	20–80	WASI	105	56 (54–58)	54 (52–56)	1.2 (−1.2 to 3.7)
		Matrix reasoning				105	54 (52–56)	54 (52–56)	−0.6 (−2.6 to 1.4)
Language	Expressive	Vocabulary				105	56 (54–58)	57 (55–59)	−0.5 (−2.4 to 1.4)
	Verbal reasoning	Similarities				105	57 (55–59)	57 (56–59)	−0.3 (−2.1 to 1.6)
Language	Receptive	Comprehension of instructions	Scaled score	1–19	NEPSY-II	104	11 (10.4–11.6)	12 (11.4–12.6)	0 (−0.7 to 0.6)
	Speeded naming	Speeded naming				97	9 (8.4–9.6)	9 (8.4–9.6)	0.4 (−0.3 to 1.1)
Attention	Attention	Commissions	T score	30–90	CPT-II	100	49 (47–51)	50 (48–52)	−0.8 (−3.6 to 2.0)

Domains	Neurocognitive Outcomes	Specific Tests	Specific Scores	Score Range	Assessment Instruments	No. of Sibling Pairs	Mean (95% CI)		
							Exposed	Unexposed	Difference, Exposed – Unexposed
		Omissions				100	50 (48–52)	48 (45–51)	2 (−0.6 to 4.6)
Executive function	Executive function	Global executive composite	T score	30–100	BRIEF	104	48 (46–50)	47 (45–49)	0.5 (−1.7 to 2.8)
	Working memory	Digit span	Scaled score	1–19	WISC-IV	104	11 (10.4–11.6)	11 (10.4–11.6)	−0.2 (−0.8 to 0.5)
	Cognitive flexibility	Condition 1	Scaled score	1–19	DKEFS Trail Making	104	10 (7.7–12.3)	10 (9.4–10.6)	0.5 (−0.2 to 1.2)
		Condition 2				104	10 (7.7–12.3)	9 (8.6–9.4)	0.4 (−0.3 to 1.2)
		Condition 3				104	10 (9.4–10.6)	10 (9.4–10.6)	0.6 (−0.2 to 1.4)
		Condition 4				104	9 (8.4–9.6)	9 (8.4–9.6)	0.5 (−0.2 to 1.3)
		Condition 5				104	9 (8.4–9.6)	9 (8.2–9.8)	0.2 (−0.6 to 1.1)
	Verbal fluency	Word generation	Scaled score	1–19	NEPSY-II	104	12 (11.4–12.6)	13 (12.4–13.6)	−1 (−1.7 to −0.3)
Behavior	Internalizing	Internalizing	T score	20–100	CBCL	102	50 (48–52)	47 (45–49)	3.2 (1.1 to 5.3)
	Externalizing	Externalizing				101	47 (45–49)	45 (43–47)	2.1 (0 to 4.2)
	Total problems	Total problems				101	47 (45–49)	45 (43–47)	2.7 (0.6 to 4.7)
	Adaptive behavior	Conceptual composite	Sum score	40–130	ABAS-II	102	104 (101–107)	106 (104–109)	−2 (−4.5 to 0.5)
		Socialcomposite				105	104 (101–107)	107 (105–109)	−3.3 (−6.1 to −0.6)
		Practical composite				101	97 (94–100)	98 (95–101)	−0.8 (−2.9 to 1.4)
		General adaptive composite				99	101 (98–104)	103 (100–106)	−1.4 (−3.6 to 0.7)

Abbreviations: ABAS-II, Adaptive Behavior Assessment System, Second Edition; BRIEF, Behavior Rating Inventory of Executive Functions; CBCL, Child Behavior Checklist; CPT-II, Continuous Performance Test II; CVLT-C, California Verbal Learning Test–Children; DKEFS, Delis-Kaplan Executive Function System; NEPSY-II, Developmental Neuropsychological Assessment, Second Edition; WASI, Wechsler Abbreviated Scale of Intelligence; WISC-IV, Wechsler Intelligence Scale for Children–Fourth Edition.

[a] All results presented were analyzed using paired *t* tests.

[b] For all instruments in this table, higher scores indicate better performance except for grooved pegboard, BRIEF, and CBCL.

Table 4

es and at Different Durations of Anesthesia Exposure

rmance IQ Score			Full-Scale IQ Score											
(95% CI)		Difference, Exposed – Unexposed (95% CI)	Mean (95% CI)		Difference, Exposed – Unexposed (95% CI)									
ed	Unexposed		Exposed	Unexposed										
03–113)	107 (101–113)	1 (−4.8 to 6.8)	112 (108–116)	111 (106–116)	1 (−4.1 to 6.1)									
04–112)	107 (102–112)	1 (−4.0 to 6.0)	111 (107–115)	110 (106–114)	1 (−3.5 to 5.4)									
02–112)	108 (104–112)	−1 (−6.8 to 4.8)	110 (105–115)	111 (107–115)	−1 (−5.8 to 3.8)									
						0–59	24	117 (111–123)	113 (108–118)	4 (−1.6 to 9.6)	113 (108–118)	113 (107–119)	0 (−6.8 to 6.8)	117 (112–122)	115 (110–120)	2 (−4 to 8)
04–112)	106 (103–108)	2 (−1.9 to 5.9)	110 (107–113)	110 (107–113)	0 (−3.4 to 3.4)									
4–106)	104 (96–112)	−4 (−8.5 to 4.5)	103 (96–110)	105 (99–111)	−2 (−8.2 to 4.2)									

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