Long-term Differences in Language and Cognitive Function After Childhood Exposure to Anesthesia

WHAT'S KNOWN ON THIS SUBJECT: Immature animals exposed to anesthetics display apoptotic neurodegeneration and long-term cognitive deficiencies. In children, studies of cognitive deficits associated with anesthesia exposure have yielded mixed results. No studies to date have used directly administered neuropsychological assessments as outcome measures.

WHAT THIS STUDY ADDS: This study examines the association between exposure to anesthesia in children under age 3 and deficits at age 10 by using a battery of directly administered neuropsychological assessments, with deficits found in language and abstract reasoning associated with exposure.

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KEY WORDS
anesthesiology, neurodevelopmental, cognitive function, neurotoxicity, language development

ABBREVIATIONS
aRR—adjusted risk ratio
CBCL—Child Behavior Checklist
CELF—Clinical Evaluation of Language Fundamentals
CELF-R—Clinical Evaluation of Language Fundamentals Receptive language score
CELF-E—Clinical Evaluation of Language Fundamentals Expressive language score
CELF-T—Clinical Evaluation of Language Fundamentals Total language score
CI—confidence interval
CPM—Raven's Colored Progressive Matrices
MAND—McCarron Assessment of Neuromuscular Development
PPVT—Peabody Picture Vocabulary
SDMT—Symbol Digit Modality Test

Drs Ing, DiMaggio, Whitehouse, Hegarty, von Ungern-Sternberg, Davidson, Wood, Li, and Sun conceived and designed the study; Drs Whitehouse, Hegarty, von Ungern-Sternberg, and Davidson acquired the data; Drs Ing, DiMaggio, Wood, Li, and Sun analyzed and interpreted the data; Dr Ing wrote the article, which was critically reviewed by Drs Ing, DiMaggio, Whitehouse, Hegarty, von Ungern-Sternberg, Davidson, Wood, Li, and Sun; Dr Ing and Ms Brady performed the statistical programming; and all authors reviewed and approved the final report.

abstract

BACKGROUND: Over the past decade, the safety of anesthetic agents in children has been questioned after the discovery that immature animals exposed to anesthesia display apoptotic neurodegeneration and long-term cognitive deficiencies. We examined the association between exposure to anesthesia in children under age 3 and outcomes in language, cognitive function, motor skills, and behavior at age 10.

METHODS: We performed an analysis of the Western Australian Pregnancy Cohort (Raine) Study, which includes 2868 children born from 1989 to 1992. Of 2608 children assessed, 321 were exposed to anesthesia before age 3, and 2287 were unexposed.

RESULTS: On average, exposed children had lower scores than their unexposed peers in receptive and expressive language (Clinical Evaluation of Language Fundamentals: Receptive [CELF-R] and Expressive [CELF-E]) and cognition (Colored Progressive Matrices [CPM]). After adjustment for demographic characteristics, exposure to anesthesia was associated with increased risk of disability in language (CELF-R: adjusted risk ratio [aRR], 1.87; 95% confidence interval [CI], 1.20–2.93, CELF-E: aRR, 1.72; 95% CI, 1.12–2.64), and cognition (CPM: aRR, 1.69; 95% CI, 1.13–2.53). An increased aRR for disability in language and cognition persisted even with a single exposure to anesthesia (CELF-R aRR, 2.41; 95% CI, 1.40–4.17, and CPM aRR, 1.73; 95% CI, 1.04–2.88).

CONCLUSIONS: Our results indicate that the association between anesthesia and neuropsychological outcome may be confined to specific domains. Children in our cohort exposed to anesthesia before age 3 had a higher relative risk of language and abstract reasoning deficits at age 10 than unexposed children. *Pediatrics* 2012;130:e476–e485

The neurotoxic effects of anesthetic exposure in developing brains are well established in animal models, with neurodegenerative changes found to be dose dependent and increased with multiple agents.[1–5] *N*-methyl-D-aspartate antagonists (such as nitrous oxide and ketamine) and γ-aminobutyric acid agonists (such as benzodiazepines, propofol, and volatile anesthetics) are thought to mediate these apoptotic effects.[6,7] In the animal model, long-term neurocognitive changes, including differences in learning, memory, motor activity, attention, and behavior during adulthood, have also been identified.[3,8–10] A window of vulnerability in rodents appears to occur during peak synaptogenesis between postnatal day 7 and 30.[3,11] In the human brain, peak synaptogenesis happens over a wider period of time, occurring in the primary sensorimotor cortex near the time of birth, temporal cortex at 9 months, and prefrontal cortex at 3 years of age.[12]

Findings from clinical studies are mixed, with some studies showing a twofold increase in cognitive disability in children with anesthetic exposure, whereas others show no association.[13–20] In studies demonstrating an association of anesthesia with disability, only children with multiple anesthetic exposures have been associated with deficits, but an effect with a single exposure has not been identified.[14,18,20]

These clinical studies have used *International Classification of Diseases, 9th Revision* diagnosis codes, standardized tests, and evaluations by parents and teachers as outcome measures, but none to date has used a battery of multiple directly assessed neuropsychological outcome measures. We therefore studied a prospective birth cohort to determine if (1) exposure to anesthesia for surgery or a diagnostic test during the first 3 years of life is associated with differences in any of a range of directly assessed neuropsychological outcomes; and (2) if the differences persist with only a single episode of anesthetic exposure.

METHODS

Data Source

We obtained data from the Western Australian Pregnancy Cohort (Raine) Study, an established birth cohort consisting of 2868 children born from 1989 to 1992, originally created to evaluate the long-term effects of prenatal ultrasound.[21] The Raine Study enrolled 2900 pregnant women at 16 to 20 weeks gestation from the major tertiary maternity hospital and nearby private practice medical centers in Perth, Western Australia. Mothers were selected for enrollment if they had sufficient proficiency in English, expected to deliver at the hospital, and intended to remain in Western Australia for follow-up.[22] The Raine Study collected detailed demographic and medical data prenatally and at birth from medical records and parental self-report. After birth, all children were assessed at 1, 2, 3, 5, 8, 10, 13, and 16 years of age. Parents were asked to keep detailed diaries of their child's medical history. During follow-up visits, parents filled out questionnaires describing illnesses and medical problems, which were coded by research staff into *International Classification of Diseases, 9th Revision* codes. There was no direct access to medical records after the perinatal period, including surgical and anesthetic records. We classified any child who had a surgical or diagnostic procedure requiring anesthesia before the age of 3 as "exposed" and the rest "unexposed." Children who missed all 3 scheduled follow-up visits from 1 to 3 years of age were deemed "missing." Demographic information for these missing children was assessed, but they were excluded from further

analysis, because data on exposure to anesthesia was not available for them. To ensure exposure to anesthesia, we reviewed the types of procedures, all of which were performed after leaving the maternity hospital. Children who were found to have diagnostic procedures not requiring anesthesia were placed in the unexposed group.

Outcome Variables

According to Raine Study protocol, at each follow-up visit, neuropsychological testing was performed. The most extensive testing occurred at the 10-year follow-up visits and consequently these tests were used as the outcome measures. A total of 6 tests were performed at age 10, and only 2 tests were performed at the other follow-up visits. The age 10 follow-up visit was the only time where language, cognitive function, motor skills, and behavior were all tested.

Neuropsychological Tests (Table 1)

Cognition was assessed by using the Symbol Digit Modality Test (SDMT) and the Raven's Colored Progressive Matrices (CPM). The SDMT assessed visual tracking, attention, and motor skills, and generated oral and written scores, whereas the CPM measured global cognitive performance, nonverbal intelligence, and visuospatial functions.[23,24] The McCarron Assessment of Neuromuscular Development (MAND) was used to measure fine and gross motor tasks.[25] The Clinical Evaluation of Language Fundamentals (CELF) is a language test that assesses higher-order semantic, grammatical, and verbal memory abilities. This test generates three scores. The CELF-R is the receptive language score and measures listening comprehension, CELF-E is the expressive language score and tracks speaking ability, and finally the CELF-T represents total language ability.[26] The

TABLE 1 Neuropsychological Tests and Descriptions

Domain	Assessment	Description
Language	Clinical Evaluation of Language Fundamentals	The child completes 3 subtests assessing expressive language and 3 assessing receptive language. Receptive tests involve listening to statements and selecting visually presented options, choosing pictures of geometric shapes in response to oral direction, and choosing 2 out of 3 or 4 orally presented words that are associated. Expressive tests include generating a sentence given a word and picture stimulus, composing intact sentences from visually and orally presented words, and repeating orally presented sentences.
	Peabody Picture Vocabulary Test	The examiner says a word and the child must choose the corresponding object from a group of 4 pictures. Items increase in difficulty.
Cognition	Raven's Colored Progressive Matrices	The child completes a multiple-choice paper test that consists of pictures that require the matching of visual patterns ranging from obvious to complex and abstract. The test is language free.
	Symbol Digit Modality Test	Symbols are printed next to numbers as a reference, and the child is required to evaluate another group of symbols and write down the corresponding numbers. The test can also be administered in an oral version with the child replying verbally.
Behavior	Child Behavior Checklist	This is a 118-item questionnaire that is completed by the parent that evaluates behavioral problems according to 8 syndrome scales. Withdrawn, anxious/depressed, and somatic complaints are grouped and scored as internalizing problems. Delinquent behavior and aggressive behavior are grouped as externalizing problems. Social problems, attention problems, and thought problems are also evaluated and expressed in the total score.
Motor function	McCarron Assessment of Neuromuscular Development	A standardized test of motor skills comprising 5 fine motor skill tests, such as picking up and moving beads, rapid controlled tapping of the fingers, as well as 5 gross motor skill tests, such as jumping, hand strength, and standing on 1 foot. The individual scores are used to determine an overall Neuromuscular Development Index (NDI) score.

Peabody Picture Vocabulary Test (PPVT) is a receptive listening vocabulary test also assessing language.[27] Behavioral problems were measured by the Child Behavior Checklist (CBCL), a questionnaire evaluating both internalizing problems such as depression and somatic complaints, as well as externalizing problems that involve conflict with others, such as aggressive behavior and rule breaking. In addition to internalizing and externalizing scores, the CBCL also generates a total behavior score.[28] As opposed to the other neuropsychological tests, in CBCL scoring, higher scores show dysfunction, with scores <60 considered normal. The CBCL was the only indirectly assessed survey test, and, because it did not require the child to be present, CBCL testing was completed at a higher rate than other tests.

Statistical Analysis

We performed bivariate analyses to evaluate demographic differences between exposed and unexposed children. Of the 6 neuropsychological tests performed, CELF, SDMT, and CBCL were each composed of subscores. In total, 11 available neuropsychological scores and subscores were assessed as potentially important outcomes at age 10. We used t tests to assess for score differences between exposed and unexposed children. For neuropsychological assessments that showed statistically significant differences between exposed and unexposed children, we used χ^2 tests to assess for an increased likelihood of clinically relevant disability. Because published disability cutoff scores were normed for American children and may not take into account nuances of language and dialectal differences in Australian children, we used score cutoffs for disability normed for this particular cohort.[29–31] As a result, clinical disability was defined as children with scores worse than 1.5 SD than the mean of the entire cohort.[32] These score cutoffs were found to be similar to those normed for American children with the exception of slightly lower CELF-E scores in our cohort. A cutoff of 1.5 SD was chosen to apply a consistent scale for all 6 assessments, which in previously published works have had clinical disability defined at various levels including 1, 1.5, or 2 SD from the mean.[32–36] We set the a priori P value to $P < .05$. For the t tests and χ^2 tests, corrections for multiple comparisons were made by using the Holm-Bonferroni method.[37] We calculated risk ratios and 95% confidence intervals (CI) to determine the strength of the association of clinical deficit with exposure. A modified multivariable Poisson regression model with robust variance was used to adjust for socioeconomic and baseline perinatal health status variables. Sex, low birth weight (<2500 g), race, income, and maternal education level were considered as potential confounder variables. Statistical analysis was performed by using SAS version 9.2 (SAS Institute, Inc., Cary, NC).

Single and Multiple Anesthetic Exposures

For single and multiple anesthetic exposure subset analysis, we reviewed each patient and procedure to ensure the accuracy of the number of exposures. In procedures that were commonly paired, such as tonsillectomies and adenoidectomies performed with myringotomies, or hydrocele repairs with circumcisions, we used data from the Raine cohort to determine if these multiple procedures were performed during the same hospital visit. Children with commonly paired multiple procedures during the same visit were classified as "single exposure," whereas children who had multiple procedures at different visits were considered "multiple exposure." We only included children with complete follow-up from age 1 to 3 in this subset analysis to ensure that the recording of a procedure was not missed because of a missed follow-up. We used χ^2 tests to assess differences in rates of disability between exposed and unexposed children in the same neurocognitive tests found to be significant in our primary analysis. We also calculated risk ratios and adjusted risk ratios to determine the strength of the association of clinical deficit with exposure.

RESULTS

The Raine cohort consisted of 2868 children, of which 260 children had no history of follow-up from ages 1 to 3 and were classified as "missing." The missing children were significantly different from the children evaluated in our cohort in most demographic categories (Table 2). The remaining 2608 children were followed up at least once from age 1 to 3. After reviewing the procedures performed on each child, 321 children were found to have had surgical procedures requiring anesthesia before their third birthday and were classified as "exposed," whereas 2287 children did not have a history of surgery and were classified as "unexposed." We noted that exposed children were similar to unexposed children, but they included a higher proportion of boys and Caucasians compared with the unexposed group.

We also evaluated and found differences between those who followed up for testing at age 10 and those who did not. Children who did not return for testing had a higher prevalence of household income <$24 000 (46% vs 34%), maternal lack of education beyond high school (53% vs 46.5%), and maternal smoking (27.2% vs 18.2%), but they had less maternal perinatal alcohol use (30.3% vs 37.2%).

At age 10, CBCL was performed in 77% of the cohort, PPVT in 58%, and remainder of the tests in 62%. The exposed children were tested at a slightly higher rate than the overall cohort with CBCL performed in 83%, PPVT in 61%, and all other tests in 67% of the cohort. In the exposed children, the surgeries and diagnostic procedures performed before age 3 ranged from myringotomies to open-heart procedures, but the vast majority were minor procedures (Table 3).

Neuropsychological Score and Risk of Disability Differences in Exposed and Unexposed Children

We evaluated all neuropsychological tests at age 10. When compared with unexposed children, we found evidence that children exposed to anesthesia had significantly worse scores in tests of receptive, expressive, and total language (CELF-R: receptive language, P = .006; CELF-E: expressive language, P = .004; CELF-T: total language, P = .003) and cognition, specifically abstract reasoning measured by CPM (P = .002) (Table 4). We did not note any differences between exposed and unexposed children in behavior and motor function domains.

To determine the clinical implications of these score differences on language and abstract reasoning, we examined differences in the incidence of clinical disability between exposed and unexposed children (Table 5). Evidence for a significantly increased rate of disability in exposed children was seen in receptive, expressive, and total language, (CELF-R, P = .0008; CELF-E, P = .005; CELF-T, P < .0001) and abstract reasoning tests (CPM, P = .01). After adjustment for confounders, we determined that children exposed to anesthesia before age 3 had a significantly increased risk of disability in receptive language (CELF-R) (adjusted risk ratio [aRR], 1.87 [CI, 1.20–2.93]), expressive language (CELF-E) [aRR, 1.72 (95% CI, 1.12–2.64)], total language (CELF-T) (aRR, 2.11 [95% CI, 1.42–3.14]) and abstract reasoning (CPM) (aRR, 1.69 [95% CI, 1.13–2.53]) (Table 6).

Single and Multiple Anesthetic Exposures

We only included the children with complete follow-up from age 1 to 3 in the single- and multiple-exposure subset analysis, which included 1781 children. Of these children, 1523 were unexposed, 206 had a single exposure, and 52 had multiple exposures. We used χ^2 tests to compare the unexposed, single-exposure, and multiple-exposure groups and found evidence that significant differences in disability existed in CELF-T (P < .0001), CELF-R (P < .0001), and CPM (P = .03) scores (Table 5). After adjusting for confounders, the aRR for disability was significant for total language (CELF-T) in single and multiple exposure (aRR, 2.36; 95% CI, 1.47–3.79 and aRR, 2.68 95% CI, 1.07–6.72, respectively), receptive language (CELF-R) for single and multiple exposure (aRR, 2.41; 95% CI, 1.40–4.17 and aRR, 3.52 95% CI, 1.38–9.00, respectively), and abstract reasoning (CPM) for single exposure (aRR, 1.73; 95% CI, 1.04–2.88) (Table 6).

TABLE 2 Birth Characteristics of Children Unexposed and Exposed to Anesthesia before 3 Years of Age

	Unexposed (n = 2287), n (%)	Exposed (n = 321), n (%)	Pa	Missing (n = 260), n (%)	Pb
Gender					
Girls	1161 (50.8)	112 (34.9)	<.0001	140 (53.9)	.12
Boys	1126 (49.2)	209 (65.1)		120 (46.2)	
Birth weight					
<1400 g	31 (1.4)	8 (2.5)	.6	14 (5.4)	.0006
1400–1999 g	39 (1.7)	7 (2.2)		3 (1.2)	
2000–2499 g	119 (5.2)	18 (5.6)		13 (5.0)	
2500–2999 g	390 (17.1)	55 (17.1)		44 (16.9)	
3000–3999 g	1503 (65.7)	202 (62.9)		156 (60.0)	
≥4000 g	197 (8.6)	31 (9.7)		28 (10.8)	
Unknown	8 (0.3)	0 (0.0)		2 (0.7)	
Apgar at 5 min					
0–6	36 (1.6)	5 (1.6)	.3	15 (5.8)	<.0001
7–10	2236 (97.8)	316 (98.4)		239 (91.9)	
Unknown	15 (0.7)	0 (0.0)		6 (2.3)	
Race					
Caucasian	1981 (86.6)	296 (92.2)	.001	196 (75.4)	<.0001
Non-Caucasian	257 (11.2)	15 (4.7)		59 (22.7)	
Unknown	49 (2.1)	10 (3.1)		5 (1.9)	
Household income (AUD)					
< $7000	164 (7.2)	23 (7.2)	.03	42 (16.2)	<.0001
$7000–$23999	709 (31.0)	111 (34.6)		106 (40.8)	
$24000 − $35999	551 (24.1)	59 (18.4)		38 (14.6)	
≥ $36000	687 (30.0)	113 (35.2)		35 (13.5)	
Unknown	176 (7.7)	15 (4.7)		39 (15.0)	
Father living at home					
Home	1950 (85.3)	272 (84.7)	.5	190 (73.1)	<.0001
Not at home	272 (11.9)	36 (11.2)		60 (23.1)	
Unknown	65 (2.8)	13 (4.0)		10 (3.9)	
Maternal education beyond high school					
None	1119 (48.9)	159 (49.5)	.4	170 (65.4)	<.0001
Trade certificate, professional registration or other	508 (22.2)	78 (24.3)		42 (16.2)	
College or university degree	611 (26.7)	74 (23.1)		43 (16.5)	
Unknown	49 (2.1)	10 (3.1)		5 (1.9)	
Maternal perinatal smoking					
No	1584 (69.3)	216 (67.3)	.6	105 (40.4)	<.0001
1–20 daily	443 (19.4)	60 (18.7)		70 (26.9)	
21 or more daily	51 (2.2)	8 (2.5)		12 (4.6)	
Unknown	209 (9.1)	37 (11.5)		73 (28.1)	
Maternal perinatal alcohol use					
Several times per week	115 (5.0)	14 (4.4)	.6	5 (1.9)	<.0001
Once a week	185 (8.1)	31 (9.7)		15 (5.8)	
Less than once a week	491 (21.4)	65 (20.2)		35 (13.5)	
Never	1266 (55.4)	172 (53.6)		130 (50.0)	
Unknown	230 (10.1)	39 (12.1)		75 (28.9)	

Because of rounding, percentages may not sum to 100. AUD, Australian dollar.

a Exposed children were compared with unexposed children with χ^2 tests.

b Missing children were compared with all other children (exposed and unexposed) with χ^2 tests.

DISCUSSION

Children who were exposed to anesthesia for surgery or diagnostic testing before age 3, compared with those who were not exposed, have an increased risk for long-term deficits in language and abstract reasoning at age 10. This increased risk was found even in children with a single exposure to anesthesia. Our findings show that not all cognitive domains are uniformly affected. There was no evidence of differences in visual tracking and attention (SDMT), fine and gross motor function (MAND), or behavior (CBCL) based on anesthesia exposure status. Interestingly, although the CELF showed clear differences in receptive language ability, we did not see any differences in the PPVT, which is also a language test of receptive vocabulary and verbal ability. The CELF, however, assesses higher-order language abilities, and it is possible that the PPVT was unable to capture those differences.[38] This finding further emphasizes the importance of using sensitive and specific neurocognitive

TABLE 3 Procedures Performed on Children Exposed to Anesthesia

Procedure	n (%)
Myringotomy	112 (24.8)
Inguinal and umbilical hernia	46 (10.2)
Circumcision	41 (9.1)
Tonsillectomy and adenoidectomy	32 (7.1)
Dental procedure	26 (5.8)
Minor skin and nail procedure	25 (5.5)
Orchiopexy, hydrocele and varicocele	19 (4.2)
Procedure on extraocular muscles	16 (3.5)
Hypo/epispadias repair and chordee release	13 (2.9)
Nasolacrimal duct probe	12 (2.7)
Procedures on mouth/tongue and cleft lip and palate repair	12 (2.7)
Gastric and bowel repair and resection	10 (2.2)
Minor rectal/anal procedure	8 (1.8)
Endoscopy and biopsy	7 (1.6)
Foot and knee surgery	7 (1.6)
Finger and hand surgery	7 (1.6)
Computed tomography scan	7 (1.6)
Nasal airway procedure	6 (1.3)
Cardiac catheterization	5 (1.1)
Lymph node excision	5 (1.1)
Procedure on orbit, lens, or retina	5 (1.1)
Open heart procedure	4 (0.9)
Kidney and urinary tract procedure	4 (0.9)
Tracheostomy	4 (0.9)
Laparotomy and laparoscopy	3 (0.7)
Appendectomy	3 (0.7)
Laryngoscopy, tracheoscopy, and bronchoscopy	2 (0.4)
Repair of aortic coarctation	2 (0.4)
Pyloromyotomy	2 (0.4)
Craniectomy	1 (0.2)
Patent ductus arteriosus closure	1 (0.2)
Bone marrow biopsy	1 (0.2)
Tenckhoff catheter placement and peritoneal dialysis	1 (0.2)
MRI	1 (0.2)
Diaphragmatic hernia repair	1 (0.2)
Total	451 (100)

Due to patients with multiple exposures, the number of procedures exceeds the number of exposed patients.

tests in assessing deficits that can result from exposure to neurotoxic agents.

The major strength of this cohort is the availability of a battery of directly administered neuropsychological assessments, which have not been used in previously published clinical studies of anesthetic neurotoxicity. In the past, outcomes such as diagnostic codes, academic performance, standardized testing, school and medical records, and parent and teacher surveys have been used.[13–18,20] Although some of these studies have found differences between exposed and unexposed children, directly administered neuro-psychological assessments may have increased sensitivity to capture subtle effects that may be difficult to detect clinically. Neurodevelopmental studies of lead, pesticides, and other potential neurotoxins have similarly found that appropriate assessment tools are critical in documenting the effects of exposure.[39,40] In neurotoxicology studies, sensitive outcomes are particularly important because an effect size of 0.2 SD can be of clinical and public health significance.[39]

The magnitude of increased relative risk of disability found in this study was consistent with that reported by other investigators. Our adjusted relative risk of clinical deficit ranged from 1.69 to 2.11, whereas DiMaggio et al[17,18] measured an adjusted hazard ratio of developmental or behavioral disorder of 2.3 (95% CI, 1.3–4.1) in exposed children, and Wilder et al[14] and Flick et al[20] found an increased risk of learning disability of 2.6 (95% CI, 1.6–4.2) and 2.12 (95% CI, 1.26–3.54), respectively. Although these studies only found a difference in children with multiple anesthetic exposures, our data indicate that, by using sensitive measures, an increased risk of cognitive disability can be demonstrated in children with a single exposure. We found the adjusted relative risk ratio of disability in the multiple-exposure children to be similar to those with a single exposure. It is possible a "dose-response" effect may become evident with a larger sample of children than is available with our study cohort. It should be noted that a much smaller number of children tested were exposed to multiple anesthetics (40 children) in comparison with the larger number exposed to only a single anesthetic (141 children) (Table 5). One caveat is that, in general, analysis of single versus multiple exposures has been used as a crude estimate for the dose of anesthetic exposure, because the duration of exposure and anesthetics agents used in procedures may vary widely. Our results, however, do suggest that a single exposure to anesthesia is associated with long-term deficits.

There are several limitations in our study. They include the retrospective nature of the analysis (however, the cognitive testing was performed prospectively and independent of the hypothesis being tested here), differences in demographics between the exposed and unexposed children, the lack of detailed anesthetic information, the assessment tool available to assess behavior, and the attrition of the cohort over time.

There were demographic differences between exposed and unexposed children. More exposed children were Caucasian and lived in higher-income households compared with the unexposed children. We also found a higher proportion of boys in the exposed group, as has been reported in previous studies.[14] However, the observed increase in risk with anesthesia exposure remained even after adjusting for the demographic variables and gender of the child in our regression model. When interpreting our results for external validity, the differences in the missing children with regard to baseline socioeconomic and perinatal health variables should be taken into account. The exclusion of non-English-speaking mothers from the study may also lead to the study findings being less relevant to children at a lower socioeconomic status.

Part of the association of neurocognitive deficit with anesthesia may be

TABLE 4 Differences Between the Mean Scores of Unexposed and Exposed Children at Age 10

Neuropsychological Domain	Neuropsychological Test Score	Unexposed Test Scores, Mean (SD)	Exposed Test Scores, Mean (SD)	Score Difference between Unexposed and Exposed	P
Language	CELF Total Score	96.2 (15.1)	92.6 (17.1)	3.7	.003[a]
	CELF Receptive Score	101.9 (15.8)	98.2 (18.1)	3.7	.006[a]
	CELF Expressive Score	91.9 (14.9)	88.3 (16.8)	3.6	.004[a]
	PPVT Standard Score	104.2 (12.1)	103.1 (12.5)	1.2	.2
Cognition	CPM Total Score	31.2 (3.6)	30.2 (4.3)	1.0	.002[a]
	Written SDMT Score	34.6 (7.5)	33.7 (7.8)	0.9	.1
	Oral SDMT Score	43.9 (10.3)	43.2 (10.7)	0.7	.4
Behavior	CBCL Total Score	47.4 (11.5)	48.7 (10.6)	1.4	.06
	CBCL Internalizing Score	49.3 (10.6)	50.2 (10.4)	1.0	.2
	CBCL Externalizing Score	47.3 (10.8)	47.8 (10.4)	0.5	.5
Motor function	MAND NDI Score	94.3 (13.8)	92.6 (14.7)	1.7	.1

NDI, Neuromuscular Development Index Score.

[a] Significant values using $P < .05$ and Holm-Bonferroni adjustment for multiple comparisons.

TABLE 5 Association of Anesthesia Exposure before Age 3 and Neuropsychological Disability at age 10

Overall Cohort, n		Disability		Single/Multiple Exposure, n		Disability	
		Disability/Total (%)	P			Disability/ Total (%)	P
CELF total	1615	CELF-T <72.6[a]		CELF Total	1235	CELF-T <72.6[a]	
Unexposed	1401	85/1401 (6.1)	<.0001[b]	Unexposed	1054	53/1054 (5.0)	<.0001[b]
Exposed	214	30/214 (14.0)		Single exposure	141	20/141 (14.2)	
				Multiple exposure	40	5/40 (12.5)	
CELF receptive	1615	CELF-R <77.2[a]		CELF receptive	1235	CELF-R <77.2[a]	
Unexposed	1401	70/1401 (5.0)	.0008[b]	Unexposed	1054	40/1054 (3.8)	<.0001[b]
Exposed	214	23/214 (10.7)		Single exposure	141	16/141 (11.3)	
				Multiple exposure	40	5/40 (12.5)	
CELF expressive	1615	CELF-E <68.6[a]		CELF expressive	1235	CELF-E <68.6[a]	
Unexposed	1401	89/1401 (6.4)	.0046[b]	Unexposed	1054	58/1054 (5.5)	.031
Exposed	214	25/214 (11.7)		Single exposure	141	14/141 (9.9)	
				Multiple exposure	40	5/40 (12.5)	
CPM total	1627	CPM <25.5[a]		CPM total	1246	CPM <25.5[a]	
Unexposed	1413	112/1413 (7.9)	.012[b]	Unexposed	1065	75/1065 (7.0)	.033[b]
Exposed	214	28/214 (13.1)		Single exposure	141	18/141 (12.8)	
				Multiple exposure	40	5/40 (12.5)	

[a] Score cutoff values used for each neuropsychological test. Set at 1.5 SD below the mean of the entire cohort.

[b] Significant values by using $P < .05$ and Holm-Bonferroni Adjustment for multiple comparisons.

due to innate differences between children requiring surgery and diagnostic procedures and those not requiring these procedures. Because we did not have access to medical records for the current study, we were unable to adjust for comorbid disease in either group. However, the fact that the vast majority of children underwent minor procedures leads us to believe that significant comorbidity is unlikely to confound our results.

The lack of access to medical records also limited our ability to review anesthetic exposure including specific drugs used and duration of anesthesia.

Because the study period was during a time when the most prevalent volatile anesthetic was halothane, we surmise that in the majority of our patients this was the agent used. Although halothane is no longer clinically available, it has been found to cause similar neurotoxic effects as other volatile anesthetics in the animal model.[41,42]

CBCL, although widely used and well validated,[16,43–45] is a behavior survey assessment completed by parents, and the only test among the 6 used not directly administered by trained research staff. Our finding of a lack of difference in behavior has also been

reported in another recent study by using an outcome that may also lack adequate sensitivity.[20] These findings may be due to a sparing of neurocognitive effects of anesthetics on behavior, or possibly the relative lack of sensitivity of this test, particularly in comparison with the other directly administered assessment tools. Other recent data, however, suggest that anesthesia exposure may be associated with attention-deficit/hyperactivity disorder.[46] This further emphasizes the need for sensitive, directly administered behavior assessments to evaluate the

TABLE 6 Risk Ratios and Adjusted Risk Ratios of Exposure to Anesthesia Before Age 3 and Disability on Neuropsychological Testing at Age 10

	Disability	
	Unadjusted, RR (95% CI)	Adjusted, aRR[a] (95% CI)
Overall cohort		
CELF Total	2.31 (1.56–3.41)	2.11 (1.42–3.14)
CELF Receptive	2.15 (1.37–3.37)	1.87 (1.20–2.93)
CELF Expressive	1.84 (1.21–2.80)	1.72 (1.12–2.64)
CPM Total	1.65 (1.12–2.43)	1.69 (1.13–2.53)
Number of exposures		
CELF total		
Unexposed (0)	Reference	Reference
Single exposure (1)	2.82 (1.74–4.57)	2.36 (1.47–3.79)
Multiple exposure (≥2)	2.49 (1.05–5.88)	2.68 (1.07–6.72)
CELF receptive		
Unexposed (0)	Reference	Reference
Single exposure (1)	2.99 (1.72–5.19)	2.41 (1.40 − 4.17)
Multiple exposure (≥2)	3.29 (1.37–7.89)	3.52 (1.38 − 9.00)
CELF expressive		
Unexposed (0)	Reference	Reference
Single exposure (1)	1.80 (1.03–3.15)	1.53 (0.88–2.66)
Multiple exposure (≥2)	2.27 (0.96–5.35)	2.35 (0.97–5.70)
CPM total		
Unexposed (0)	Reference	Reference
Single exposure (1)	1.81 (1.12–2.94)	1.73 (1.04–2.88)
Multiple exposure (≥2)	1.78 (0.76–4.15)	1.92 (0.81–4.55)

RR, risk ratio.

[a] Adjusted risk ratios (aRR) adjusted for sex, low birth weight (<2500 g), race, income, and maternal education.

existence of subtle neuropsychological differences.

The geographically isolated nature of Western Australia is likely to result in less migration than other parts of the world, but like any cohort study, we experienced loss to follow-up. In our overall cohort, children who were exposed to anesthesia and did not follow-up at ages 1, 2, or 3 could be misclassified as unexposed children. This would likely bias the result toward the null, or a lack of a difference between exposed and unexposed children.

If this is the case, the differences that we found may in fact be underestimating the true difference between exposed and unexposed children.

CONCLUSIONS

In this birth cohort, children exposed to anesthesia before age 3 had an increased long-term risk of clinical deficit in receptive and expressive language, as well as abstract reasoning. Children who only had a single exposure to anesthesia also had an increased risk of deficit in receptive language and

abstract reasoning. Our results indicate that the association between anesthesia and neurodevelopmental outcome may be confined to specific domains. Our study documented specific deficits obtained through directly administered neuropsychological assessment. This is in contrast to earlier studies finding no evidence of an association using broad-based summary scores, but in line with more recent data finding exposure to anesthesia associated with learning disability and receipt of individualized education programs for speech/language impairment.[13,15,16,19,20] Our findings may play an important role in directing future studies by identifying deficits in specific neuropsychological domains associated with anesthetic exposure. It is also noteworthy that the outcomes of language and reasoning cannot be easily assessed in the animal model, which emphasizes the importance of studies in humans.

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