Neurodevelopmental Assessment in Kindergarten in Children Exposed to General Anesthesia before the Age of 4 Years

A Retrospective Matched Cohort Study

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ABSTRACT

Background: Animal studies demonstrate general anesthetic (GA) toxicity in the developing brain. Clinical reports raise concern, but the risk of GA exposure to neurodevelopment in children remains uncertain.

Methods: The authors undertook a retrospective matched cohort study comparing children less than 4 yr of age exposed to GA to those with no GA exposure. The authors used the Early Development Instrument (EDI), a 104-component questionnaire, encompassing five developmental domains, completed in kindergarten as the outcome measure. Mixed-effect logistic regression models generated EDI estimates for single *versus* multiple GA exposure and compared both single and multiple exposures by the age of 0 to 2 or 2 to 4 yr. Known sociodemographic and physical confounders were incorporated as covariates in the models.

Results: A total of 18,056 children were studied: 3,850 exposed to a single GA and 620 exposed to two or more GA, who were matched to 13,586 nonexposed children. In children less than 2 yr of age, there was no independent association between single or multiple GA exposure and EDI results. Paradoxically, single exposure between 2 and 4 yr of age was associated with deficits, most significant for communication/general knowledge (estimate, −0.7; 95% CI, −0.93 to −0.47; $P < 0.0001$) and language/cognition (estimate, −0.34; 95% CI, −0.52 to −0.16; $P < 0.0001$) domains. Multiple GA exposure at the age of 2 to 4 yr did not confer greater risk than single GA exposure.

Conclusions: These findings refute the assumption that the earlier the GA exposure in children, the greater the likelihood of long-term neurocognitive risk. The authors cannot confirm an association between multiple GA exposure and increased risk of neurocognitive impairment, increasing the probability of confounding to explain the results. **(Anesthesiology 2016; 125:667-77)**

ANIMAL studies provide convincing evidence that general anesthesia (GA) is toxic to the developing brain during a species-specific vulnerable period and is associated with long-term neurocognitive deficits.[1–4] These findings have generated considerable concern, but the clinical relevance continues to be uncertain.[5–7] The period of potential vulnerability for human brain development is longer than it is for animals, but an age of specific risk has not been clearly defined. Dose, duration, and frequency of anesthetic exposure that may be detrimental to humans are unknown. A specific outcome measure that describes a human correlate to the histopathologic and behavioral impairments observed in animals remains undefined, and confounders are present clinically that may independently contribute to neurodevelopmental abnormalities.

Relevant clinical studies comprise a small proportion of the total number of children potentially at risk. Two recent meta-analyses of previous epidemiologic studies[8,9] determined a similar pooled hazard ratio (HR) of 1.25 (95% CI, 1.13 to 1.38) and 1.28 (95% CI, 1.1 to 1.45) for the association of anesthesia/surgery with an adverse behavioral

What We Already Know about This Topic

- The risk of general anesthesia and surgery to neurodevelopment in children remains uncertain

What This Article Tells Us That Is New

- In a Canadian retrospective cohort review of 3,850 children exposed to a single general anesthetic, 620 exposed to two or more, and over 13,000 nonexposed children, there was no association between anesthesia at age less than 2 yr and the Early Development Instrument assessment
- In children between 2 and 4 yr of age, single and multiple anesthetic exposures were associated with decreases in the Early Development Instrument score although this might be related to confounding

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or developmental outcome in children exposed to a single anesthetic before the age of 4 yr. Meta-regression suggests that the number of exposures before the age of 4 yr (HR, 1.75; 95% CI, 1.31 to 2.33) but not the age at exposure is the most significant risk factor for neurodevelopmental impairment.[8] Zhang *et al.*[9] propose that the age of specific risk is more likely less than 3 yr. A number of issues complicate the interpretation of these results: (1) the age range of exposed children in individual studies varies from birth to 4 years; (2) birth years comprise a broad era of anesthetic management and monitoring; and (3) neurodevelopmental assessments occur up to 16 yr post GA and include diverse outcome measures that may not underlie linked neurocognitive domains.

Interim results of the first prospective, randomized controlled study comparing GA to regional anesthesia for infants undergoing inguinal hernia repair support a lack of deleterious outcomes associated with a single anesthetic exposure during infancy,[10] but definitive results of this trial will not be available for a number of years. The recently published PANDA (Pediatric Anesthesia and Neurodevelopment Assessment) trial also reports no difference in domain-specific cognitive function in healthy children undergoing hernia repair before the age of 3 yr compared to healthy siblings with no exposure.[11] However, these two studies are limited to a single anesthetic exposure in children undergoing hernia repair. As such, additional alternative research efforts, which include a sufficient number of patients of defined ages, undergoing a variety of procedures, with control for known confounding variables and clearly defined outcome measures are warranted.

Accordingly, we undertook a large retrospective matched cohort study, to compare children exposed to GA and surgery before the age of 4 yr, to children with no GA/surgery exposure. Our primary endpoint was the impact of GA on specific neurodevelopmental domains, using the Early Development Instrument (EDI) assessment administered in kindergarten. We hypothesized that EDI scores would not differ in children exposed to a single GA before the age of 4 yr compared to nonexposed children. Our secondary endpoints were to compare EDI scores with single *versus* multiple GA exposure and by age at exposure to determine if multiple GA exposures confer greater neurodevelopmental risk and if there is an age of exposure before which risk is greatest.

Materials and Methods

Population and Study Design

This study was approved by the University of Manitoba (Winnipeg, Manitoba, Canada) Research Ethics Board and the Province of Manitoba's Health Information Privacy Committee (Winnipeg, Manitoba, Canada; August 2013), both of which waived the need for patient consent. All data were derived from the Manitoba Population Health Research Data Repository that houses province-wide data from several governmental ministries including health, social services, and education. Health data comprise records of all interactions in a single-payer healthcare system and include hospital discharge abstracts and physician billings. Social services data include information on receipt of government income assistance (IA) and involvement with child welfare services. Education data include student assessments in the provincial public school system. Neighborhood sociodemographic data come from the Canadian Census, available at a 400 to 700 person area level. Individual-level linkages across data sets and over time used scrambled unique identification numbers. The validity and utility of the information in the repository have been well documented.[12,13]

The study group consisted of all children who had continuous provincial health insurance coverage from birth to the end of their fifth year in the Province of Manitoba, Canada, and had undergone educational assessment using the EDI in consecutive test years 2006, 2007, 2009, and 2011. These years were chosen to encompass an era of modern anesthesia management with complete test results available. Children receiving GA until their fourth birthday were matched up to 3:1 with children not receiving GA. Hard matching was done on the following variables: birth year, sex, mother's age at birth of her first child (in 5-yr intervals), income quintile (1 and 2 *vs.* 3, 4, and 5), and urban (population more than 50,000) *versus* rural residence as sociodemographic and gender factors are known to significantly influence educational outcomes.[14–16]

GA exposure was captured from physician billing codes and hospital abstracts: before 2004, we used International Classification of Disease (ICD), Ninth Revision–Clinical Modification codes indicating a surgical procedure requiring GA; from 2004 onward, we used ICD, Tenth Revision–CA (Canada) codes specific for GA. We validated cases and matches based on the presence of physician billing codes for anesthesia ± 1 day around surgery date and absence of codes up to 4 yr for the matches.

Exclusion Criteria

We excluded children without continuous health coverage from birth to 5 yr and those with developmental disabilities (DD) diagnosed at any time in the first 5 yr. DDs were identified using three data sources: Hospital Discharge Abstracts using diagnostic codes specific for disabilities, physician billing diagnostic codes, and special needs data from education. The flow chart in figure 1 displays the elimination of cases based on these exclusions.

Outcome Measure

The EDI is a 104-component questionnaire completed by kindergarten teachers for every student in the public school system in the second half of the school year. It is a measure of school readiness in five core areas of early child development: physical health and well-being, language and cognitive development, social competence, emotional maturity, and communication skills and general knowledge. Children are scored between 0 and 10 in each core area, resulting in

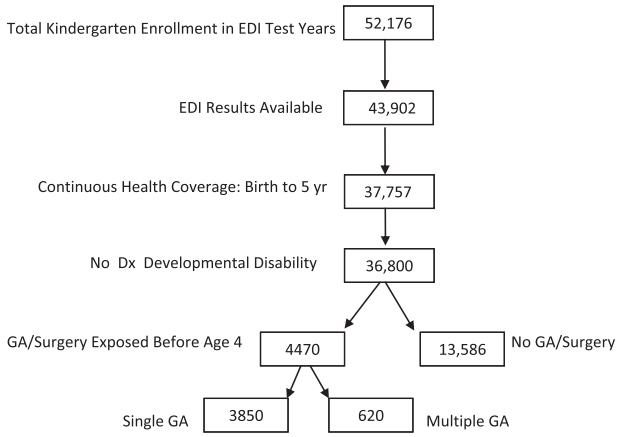

Fig. 1. Flow chart depicting the elimination of cases based on available Early Development Instrument (EDI) test results and exclusion criteria. Dx = diagnosis; GA = general anesthesia.

a combined total score of 0 to 50. Approximately 10,000 children are evaluated in the province biannually. Extensive research has confirmed EDI reliability, validity, and predictive value regarding future educational achievement.[17–24]

Confounders

Socioeconomic, demographic, and indices of health status in the year before GA exposure and the year before EDI assessment were considered potential confounders. The following factors were included as covariates in the mixed logistic regression models: ever received IA; ever involved with the child welfare system (*i.e.*, Child and Family Services); child's birth characteristics, including gestational age, small for gestational age (less than tenth percentile by sex and gestation), large for gestational age (more than 90th percentile by sex and gestation), mother's age at birth of her first child, and child's age on March 31 in the year of EDI. As an index of health status, we used the Johns Hopkins Resource Utilization Band (RUB) in the year before GA exposure and the year before EDI assessment.[25,26] The RUB system characterizes population health based on available medical and hospital claims and assigns all ICD codes to 1 of 32 diagnosis clusters that predict the need for healthcare resources over time. Clusters are then grouped into RUBs based on levels of health resource utilization regardless of underlying classification or specific disease, where 0 = no use, 1 = healthy user, 2 = low utilization, 3 = moderate utilization, 4 = high utilization, and 5 = very high utilization.

Statistical Analysis

For categorical variables, children receiving GA were compared to those not receiving GA using chi-square analysis and Fisher exact test. Continuous variables were tested for normality using the Kolmogorov–Smirnov test, presented as median and interquartile range and compared using unpaired *t* tests. All reported *P* values were two sided.

For analysis of the EDI domain and total scores, we used mixed-effect models (multilevel models) to generate regression parameter estimates with 95% CIs. These models take into account the correlated nature of the data when using matched sets of exposed and unexposed children. Specifically, each set of one exposed child and their corresponding matched unexposed children (up to three) was treated as a cluster. These clusters served as the second level in the mixed model. Two models were constructed *a priori*: (1) comparing single GA *versus* multiple GA *versus* no GA exposure for the entire cohort and (2) comparing single GA exposure by age 0 to 1, 1 to 2, 2 to 3, and 3 to 4 yr at exposure. A third model comparing multiple GA exposures restricted by ages 0 to 2 *versus* 2 to 4 yr was constructed *a posteriori*, based on initial results. To adjust for multiple comparisons, significance was accepted at the $P < 0.0025$ level, corresponding to a conservative correction of 20 comparisons per model. All analyses were performed using SAS version 9.4 (SAS Institute, USA). Mixed models were run with PROC MIXED in the SAS/STAT suite of procedures.

Results

Our initial cohort consisted of 36,800 children who had continuous health coverage and no diagnosis of a DD from birth to 5 yr for whom EDI scores were available in assessment years 2006, 2007, 2009, and 2001 (fig. 1). Of these, 4,470 (11.7%) children were exposed to GA before the age of 4 yr (3,850 single and 620 multiple GA exposures). A total of 2,664 (59.6%) exposed children were boys. We were able to find three matches for 2,651 children (59.3%), two matches for 1,382 children (30.92%), and one match for 394 children (8.8%). Only 43 cases were unable to be matched (0.96%). Thus, the final sample for analysis consisted of 18,056 children of whom 3,850 were exposed to a single GA, 620 exposed to two or more GA, and 13,586 with no GA exposure.

Descriptive statistics are shown in table 1. Children exposed to GA before the age of 4 yr were more likely to be born prematurely or large for gestational age and to have more health issues as manifest by higher RUB level in the year before GA exposure and the year before EDI. They were also more likely to come from families who had ever required IA or who had ever been taken into care by the child welfare system. The child's age on March 31 in the year of EDI assessment was not different between groups. Due to the large sample size and resulting power to detect differences between the groups, standardized differences were also calculated for each of these variables. Differences between the exposed and unexposed samples were typically quite small (less than 0.20), with several meeting the standard as negligible (less than 0.10).[27] Nevertheless, these variables were included in the regression models, so that the any measurable confounding could be fully accounted for.

The distribution of cases by surgical specialty is shown in table 2. The majority of cases consisted of dental, general surgery, and ear, nose, and throat procedures. However, children 0 to 2 yr were more likely to undergo ear, nose and throat and general surgical procedures, while the preponderance of procedures in the children 2 to 4 yr consisted of

Table 1. Comparison of Exposed *versus* Nonexposed Children

	GA, n (%)	No GA, n (%)		
Age range (yr)				
0–1	406 (10.5)	954 (10.0)		
1–2	756 (19.6)	1,965 (20.5)		
2–3	1,192 (31.0)	2,980 (31.1)		
3–4	1,496 (38.9)	3,670 (38.4)		
Total	3,850 (100)	9,569 (100)		
Categorical Variables			Standard Difference	*P* Value
Gestation ≤ 36 wk	345 (9.0)	508 (5.3)	0.14	< 0.001
SGA	257 (6.7)	648 (6.8)	0.004	0.87
LGA	678 (17.6)	1,428 (14.9)	0.07	< 0.001
RUB before GA				
0	124 (3.2)	780 (8.2)	0.21	< 0.001
1	492 (12.8)	1,741 (18.2)	0.15	<0.001
2	1,371 (35.6)	3,939 (41.2)	0.11	< 0.001
3	1,576 (40.9)	2,857 (29.9)	0.23	< 0.001
4 or 5	287 (7.5)	252 (2.6)	0.22	< 0.001
RUB before EDI				
0	382 (9.9)	920 (9.6)	0.04	< 0.001
1	924 (24.0)	2,904 (30.4)	0.14	< 0.001
2	1,758 (45.7)	4,349 (45.5)	0.004	< 0.001
3	720 (18.7)	1,357 (14.2)	0.12	< 0.001
4 or 5	66 (1.7)	39 (0.4)	0.13	< 0.001
Income assistance	1,758 (45.7)	3,670 (38.3)	0.15	< 0.001
CFS	307 (8.0)	645 (6.7)	0.05	0.01
Continuous Variables	GA, Median (IQR)	No GA, Median (IQR)		*P* Value†
Gestation (wk)	39.0 (2.0)	40 (1.0)	0.16	< 0.0001
Mother's age at first birth (yr)	22.1 (8.3)	22.7 (8.4)	0.06	0.008
Age on March 31, yr of EDI (yr)	5.8 (0.5)	5.8 (0.5)	0.009	0.6

*Compared by Fisher exact. †Compared by Student's *t* test.

CFS = Child and Family Service Involvement; EDI = Early Development Instrument; GA = general anesthesia; IQR = interquartile range; LGA = large for gestational age; RUB = Resource Utilization Band (index of health status); SGA = small for gestational age.

dental restorations (57%). Tympanostomy tube placement accounted for 33.1% of all cases in children 0 to 2 yr and for 10% of all cases in children 2 to 4 yr.

Model 1: Single versus *Multiple GA Exposure*

This model compared EDI scores with single (n = 3,850) *versus* multiple (n = 620) *versus* no GA (n = 13,586) exposure for the entire cohort. All potential confounders were included as covariates in this and each subsequent model. The complete model results generated for the communication/general knowledge domain can be found in the Supplemental Digital Content (http://links.lww.com/ALN/B298).

Table 3 shows EDI scores and estimates generated from this model. When analyzed as an entire cohort, both single and multiple GA exposures had a small but significant negative effect on the estimates for total EDI scores and for communication/general knowledge, language/cognition, and physical domains.

Table 2. Surgical Cases

	Total, n (%)	Age 0–2 yr, n (%)	Age 2–4 yr, n (%)
Dental	1,755 (38.4)	106 (6.1)	1,649 (56.8)
Ear, nose, and throat	1,133 (24.8)	550 (35.7)	583 (21.1)
General surgery	655 (14.3)	432 (28.9)	223 (8.4)
Ophthalmology	189 (4.1)	94(5.6)	95 (3.1)
Orthopedics	188 (4.1)	79 (4.5)	109 (3.4)
Plastic surgery	167 (3.8)	95 (6.1)	72 (2.5)
Urology	256 (5.6)	169 (10.3)	87 (3.0)
Neurosurgery/other	95 (2.1)	47 (3.0)	48 (1.7)

Table 3. Early Development Instrument Results: Single *versus* Multiple GA

			Single GA (n = 3,850)					Multiple GA (n = 620)			
	No GA		Mixed-effect Model					Mixed-effect Model			
Domain	EDI Score (SD)	EDI Score (SD)	Estimate	95% CI	*t* Value	*P* Value	EDI Score (SD)	Estimate	95% CI	*t* Value	*P* Value
Com/gen knowl	7.6 (2.6)	7.1 (2.8)	−0.35	−0.45 to 0.26	−7.6	< 0.0001	6.9 (2.8)	−0.49	−0.69 to −0.28	−4.6	< 0.0001
Emotional maturity	7.8 (1.6)	7.6 (1.6)	−0.06	−0.12 to −0.007	−2	0.03	7.6 (1.6)	−0.04	−0.17 to 0.08	−0.68	0.49
Lang/cogn development	8.1 (2.0)	7.7 (2.3)	−0.23	−0.3 to −0.16	−6.37	< 0.0001	7.6 (2.4)	−0.3	−0.46 to −0.14	−3.62	< 0.0001
Physical well-being	8.7 (1.4)	8.4 (1.6)	−0.14	−0.19 to −0.09	−5.59	< 0.0001	8.3 (1.7)	−0.25	−0.36 to −0.13	−4.23	< 0.0001
Social competence	8.2 (1.8)	8.0 (2.0)	−0.1	−0.17 to −0.04	−3.06	0.002	7.9 (2.0)	−0.14	−0.29 to 0.009	−1.84	0.06
Total score	40.2 (7.7)	38.7 (8.4)	−0.87	−1.13 to −0.6	−6.45	< 0.0001	38.3 (8.6)	−1.2	−1.83 to −0.61	−3.94	< 0.0001

Lower and upper refer to 95% CI; significance accepted at $P < 0.0025$ for multiple comparisons.

Com/gen knowl = communication/general knowledge; Estimate = estimate for independent effect of single or multiple general anesthesia (GA) on Early Development Instrument (EDI) score using mixed model regression; Lang/cogn development = language/cognitive development.

However, confidence limits of the estimates demonstrate overlap between single and multiple exposures and comparisons of the single *versus* multiple GA exposure estimates were not significantly different for any domain (*e.g.*, total score: single GA *vs.* multiple GA estimate = 0.2 [95% CI, 0.43 to 0.83; $P = 0.54$]).

Table 4 shows the relative significance of GA exposure compared to the other covariates included in this model using total EDI scores as representative for the results for each domain. The average impact of each covariate on EDI scores is indicated by the size of the covariate estimate. Relative impact of the covariates can be estimated by examining the individual *F* values. Social factors (IA, Child and Family Services, and mother's age at first birth) had the greatest impact on total EDI score, followed by gestational age. For comparison, the effect of IA on the estimate for total EDI score was three times greater than that of GA exposure, while the corresponding *F* value was 20 times higher than that of GA exposure. Overall, the impact of GA on EDI scores was similar to that of the physical morbidity measures (RUB 4 or 5)—*i.e.*, significant, but much smaller than for the social factors.

Model 2: Single Exposure: Age Interaction

This model included the interaction between age (in years) at GA exposure and GA exposure status. Children were stratified by age as 0 to 1, 1 to 2, 2 to 3, or 3 to 4 yr. Ages 0 to 1 and 1 to 2 yr were combined to provide comparable numbers in each age group. The interaction of age by GA exposure was significant for total score and every EDI domain except emotional maturity. That is, the effect of GA was dependent on the child's age at GA exposure (*e.g.*, total score: $F = 13.58$; $P < 0.0001$). For children 0 to 2 yr, GA exposure was not associated with significant differences in EDI scores. For children 2 to 4 yr, GA exposure had a significant negative association with EDI scores in every domain except emotional maturity. Comparison of test scores and estimates by age at single GA exposure are shown in table 5.

Model 3: Multiple GA Exposure: Age Interaction

This model compared children in whom multiple GA exposure occurred exclusively before or after the age of 2 yr. We report on 268 total cases with these restricted criteria: age 0 to 2 yr (multiple GA: n = 90 *vs.* no GA: n = 220); age 2 to 4 yr (multiple GA: n = 178 *vs.* no GA: n = 446). Of the children with multiple exposures, the majority ($n = 233$) had two GA exposures, 25 patients had three GA exposures, and 10 patients had 4 or more exposures. Similar to the single-exposure model, the interaction between GA and age at GA exposure was significant for total EDI score and two domains (*i.e.*, communication and general knowledge and physical well-being). Again, GA exposure was negatively associated with EDI score only for the older children (2 to 4 yr) in the cohort. Multiple exposures under the age of 2 yr had no significant association with EDI scores. Comparison of test scores and estimates by age at multiple GA exposure are shown in table 6.

Discussion

When analyzed as a single cohort, our results corroborate earlier studies that suggest that a single anesthetic exposure before the age of 4 yr is associated with small but statistically significant neurodevelopmental deficits, most evident in communication/general knowledge and language/cognitive domains.[26,28] When the analysis is stratified by age, however, the overall negative neurodevelopmental findings are entirely accounted for by children exposed to GA between 2 and 4 yr of age. EDI scores were not different in any domain with GA exposure in children from birth to 2 yr. Although the total number of children in this younger age group was less than the older cohort, the lack of association between GA exposure and EDI scores is unlikely to be explained by a lack of adequate power, as the effect size for any outcome difference in this group of children was negligible. We are not able to confirm an increased risk with multiple GA exposure.

Table 4. Comparison of Covariate Effects

	Mixed-effect Model			
Covariate	Estimate	95% CI	*F* Value	*P* Value
Any GA	−1.2	−1.83 to −0.61	26.1	< 0.0001
Income assistance	−3.17	−3.45 to −2.9	511.7	< 0.0001
CFS involvement	−2.94	−3.4 to −2.5	157.5	< 0.0001
Mother's age at birth first child	0.15	0.13 to 0.18	152.1	< 0.0001
Gestational age	0.18	0.12 to 0.25	32.9	< 0.0001
RUB 4–5 (pre-EDI)	−3.35	−4.5 to −2.7	17.3	< 0.0001
RUB 4–5 (pre-GA)	−1.14	−1.7 to −0.58	8.9	< 0.0001
SGA	−0.59	−1.02 to −0.16	7.4	0.007
LGA	0.13	−0.17 to 0.42	0.7	0.49

Lower and upper refer to 95% CI; significance accepted at $P < 0.0025$ for multiple comparisons.

CFS = Child and Family Services; Estimate = estimate for independent effect of covariate on Early Development Instrument (EDI) score using mixed model regression; GA = general anesthetic; LGA = large for gestational age; RUB = Resource Utilization Band (Index of health status); SGA = small for gestational age.

Table 5. Early Development Instrument Results: Single GA Exposure by Age

	EDI Score (SD)		Mixed-effect Model			
Age (yr)	No GA	Single GA	Estimate	95% CI	*t* Value	*P* Value
Communication and general knowledge						
0–1	7.6 (2.6)	7.5 (2.7)	0.005	−0.17 to 0.18	0.05	0.95
1–2	7.7 (2.6)	7.6 (2.7)				
2–3	7.5 (2.5)	6.9 (2.8)	−0.46	−0.7 to −0.22	−3.7	0.0002
3–4	7.6 (2.6)	6.8 (2.8)	−0.7	−0.93 to −0.47	−5.97	< 0.0001
Emotional maturity						
0–1	7.7 (1.5)	7.7 (1.7)	−0.02	−0.13 to 0.08	−0.4	0.69
1–2	7.9 (1.6)	7.8 (1.6)				
2–3	7.8 (1.5)	7.6 (1.6)	−0.061	−0.21 to 0.08	−0.83	0.59
3–4	7.8 (1.6)	7.6 (1.6)	−0.15	−0.29 to −0.015	−2.18	0.03
Language and cognitive development						
0–1	8.1 (1.9)	8.0 (2.2)	−0.06	−0.19 to 0.08	−0.9	0.38
1–2	8.1 (2.1)	8.0 (2.1)				
2–3	8.0 (2.0)	7.6 (2.3)	−0.24	−0.42 to −0.05	−2.54	0.01
3–4	8.1 (2.0)	7.6 (2.3)	−0.34	−0.52 to −0.16	−3.78	0.0002
Physical well-being						
0–1	8.7 (1.4)	8.6 (1.6)	0.02	−0.08 to 0.11	0.33	0.74
1–2	8.7 (1.4)	8.7 (1.5)				
2–3	8.6 (1.4)	8.4 (1.6)	−0.18	−0.32 to 0.05	−2.71	0.007
3–4	8.7 (1.4)	8.3 (1.6)	−0.3	−0.42 to −0.18	−4.71	< 0.001
Social competence						
0–1	8.2 (1.8)	8.1 (1.9)	0.03	−0.09 to 0.15	0.45	0.69
1–2	8.2 (1.9)	8.2 (2.0)				
2–3	8.2 (1.8)	7.9 (2.0)	−0.15	−0.32 to 0.02	−1.77	0.08
3–4	8.2 (1.8)	7.8 (2.0)	−0.28	−0.44 to −0.11	−3.33	0.0009
Total score						
0–1	40.5 (7.4)	39.9 (8.3)	−0.004	−0.51 to 0.5	−0.02	0.99
1–2	40.6 (7.9)	40.2 (8.1)				
2–3	40.1 (7.5)	38.5 (8.4)	−1.13	−1.83 to −0.44	−3.2	0.0014
3–4	40.4 (7.7)	38.1 (8.4)	−1.75	−2.42 to −1.09	−5.19	< 0.0001

Lower and upper refer to 95% CI; significance accepted at $P < 0.0025$ for multiple comparisons.

Estimate = estimate for independent effect of single general anesthesia (GA) on Early Development Instrument (EDI) score using mixed-model regression.

The current study refutes the assumption that the earlier the GA exposure, the greater the likelihood of long-term neurodevelopmental risk.[29,30] Indeed, our results contradict previous findings by showing that earlier exposure confers no significant risk, while exposure between the ages of 2 and 4 yr does.[9] The implication is that either the vulnerable period for GA-associated neurotoxicity occurs at a later stage of brain development in children than the presumed analogous

Table 6. Early Development Instrument Results: Multiple Exposures by Age

	EDI Score (SD)		Mixed-effect Model			
	No GA	Multiple GA	Estimate	95% CI	*t* Value	*P* Value
Age 0–2 yr (n = 90)						
Com/gen knowledge	7.7 (2.5)	7.5 (2.8)	0.06	−0.47 to 0.59	0.23	0.82
Emotional maturity	7.9 (1.5)	7.8 (1.6)	0.11	−0.21 to 0.45	0.7	0.48
Language/cognitive	8.3 (1.8)	8.2 (2.2)	0.2	−0.2 to 0.6	0.96	0.34
Physical well-being	8.7 (1.4)	8.7 (1.4)	0.1	−0.19 to 0.39	0.69	0.49
Social competence	8.4 (1.8)	8.3 (2.0)	0.19	−0.19 to 0.57	0.97	0.33
Total score	40.9 (7.3)	40.5 (8.4)	0.68	−0.87 to 2.2	0.86	0.39
Age 2–4 yr (n = 178)						
Com/gen knowledge	7.6 (2.7)	6.6 (3.0)	−0.84	−1.22 to −0.45	−4.3	< 0.0001
Emotional maturity	7.9 (1.6)	7.6 (1.6)	−0.12	−0.36 to 0.11	−1.06	0.29
Language/cognitive	8.1 (2.0)	7.6 (2.3)	−0.36	−0.66 to −0.06	−2.4	0.02
Physical well-being	8.8 (1.3)	8.2 (1.7)	−0.36	−0.57 to −0.15	−3.3	0.0009
Social competence	8.3 (1.8)	7.9 (2.1)	−0.2	−0.47 to 0.07	−1.45	0.15
Total score	40.7 (7.5)	37.8 (8.9)	−2	−3.1 to −0.87	−3.48	0.0005

Lower and upper refer to 95% CI; significance accepted at $P < 0.0025$ for multiple comparisons.

Com/gen = communication/general; Estimate = estimate for independent effect of multiple general anesthesia (GA) on Early Development Instrument (EDI) score using mixed model regression; Language/cognitive = language/cognitive development.

vulnerable period in animals, or time and/or inherent neuroplasticity may mitigate the detrimental effect of exposure at earlier ages. Alternatively, unknown and/or residual confounding by indication cannot be ruled out.

Age at Exposure

A central assumption underlying GA-associated neurotoxicity is the presence of a species-specific period of vulnerability during the period of rapid synaptogenesis, which occurs early in brain development.[31–33] This notion is likely an oversimplification, as areas of the brain develop at differing paces, and multiple other neuromodulatory processes may be involved.[6,32–35] However, the period of vulnerability to GA-induced neuroapoptosis and neuromodulation in the immature rat brain (postnatal day 1 to 14) coincides with the analogous critical stage of primate development (last quarter of gestation to shortly after birth).[34] If the animal data apply to humans, then the analogous period of human brain development at greatest risk for neurotoxic effects corresponds to the perinatal period between the third trimester and 6 months postnatally[29,33] although synaptogenesis may continue up to 3 to 4 yr.[30,36] As such, one would expect that younger children would manifest equal, if not greater, risk than older children.[29] Our findings call this assumption into question and may account for previous discrepant findings based on age.

Four previous studies with GA exposure restricted to children under 2 yr report no significant detrimental effects on academic achievement scores.[37–40] Both Wilder *et al.*[30] in a small subanalysis of children under 2 yr and Flick *et al.*[41] provide evidence that multiple but not single GA exposure is associated with an increased odds ratio for the development of a learning disability, but did not account for potential confounders. Stratmann *et al.*[42] document decreased recognition memory in a small group of children exposed to GA at less than 1 yr.

Investigators suggest that standardized tests of academic achievement may lack the sensitivity to detect subtle differences in specific neurocognitive domains,[28] and/or single anesthetic exposure may not be sufficient to induce changes detectable by the outcome measures chosen.[43] Our findings refute this notion in children under 2 yr as no effect was present in the specific neurodevelopmental domains deemed to be of greater sensitivity[28] even with multiple GA exposures. The estimates generated by the mixed-model analysis relative to the SD of EDI score provide an indication of the effect size for the association of GA exposure with EDI results by age. The range of effect sizes for individual EDI domains in children 0 to 2 yr exposed to a single GA was 0.0005 to 0.02 SD. The corresponding effect sizes for children 2 to 4 yr were 0.09 to 0.27 SD, at least a 10-fold difference. These negligible effect sizes suggest that despite the smaller number of children in the 0- to 2-yr range, inadequate power is unlikely to account for the lack of significant association between GA exposure and EDI scores in this younger cohort.

More consistent negative neurocognitive associations have been reported in studies where the age of exposure extends to 3 or 4 yr.[28,30,44] Wilder *et al.*[30] report an increased risk for the subsequent diagnosis of a learning disability in children exposed to multiple but not single GA before the age of 4 yr, where more than 50% of the cohort were older than 2 yr. Ing *et al.*[28] report a significant association between a single anesthetic exposure before the age of 3 yr and decreased performance in directly administered neuropsychological tests of language and cognition—comparable to our results in children over 2 yr. As the earlier studies did not stratify their results by age, their findings may also be weighted to the older children in their cohort.

Multiple Exposures

Using multiple GA exposure as a surrogate for increasing dose/duration, one meta-analysis appears to demonstrate a dose–response relationship consistent with GA-related neurotoxicity.[8] These findings are based on the results of three studies with a combined n less than 400 and poor control for confounders. We provide outcome data on more than 600 children exposed to multiple GA, using domain-specific outcome measures and greater control for known confounders. Within the limits of a retrospective administrative data set, and without direct access to anesthetic records to provide definitive GA durations, we are unable to confirm increased risk with multiple *versus* single GA exposure using EDI scores as the outcome measure. This holds true when analyzing the group as a whole or when the analysis was stratified to children 0 to 2 or 2 to 4 yr. Two previous studies were also unable to confirm an increased risk with multiple GA exposure.[28,42] Our analysis may be underpowered to detect potential subtle differences with multiple GA exposure although the clinical relevance becomes questionable given the minimal difference in effect size seen.

We are left with no evidence for a causal relationship between GA exposure and subsequent EDI-based neurodevelopmental deficits among children exposed before the age of 2 yr. Animal models upon which these concerns are based do not provide a plausible neurodevelopmental mechanism to account for greater susceptibility during a later *versus* earlier period of rapid brain growth. Evidence to suggest that subsequent factors may mitigate the negative neurocognitive effects of early GA exposure is derived from rodent studies in which the negative GA-induced learning effects were modified by environmental enrichment.[45] The design of this retrospective review precludes this as an explanation for the lack of effect in children 0 to 2 yr although the greater complexity and longer time period of human brain development raises the possibility of remodeling and/or repair, given sufficient time between exposure and testing. Future studies are required to answer this question.

Confounding by Indication

Table 4 provides confirmation of the major impact of both sociodemographic and physical factors on neurocognitive development. Despite accounting for these measures in the model analysis, residual confounding due to these major influences or additional unknown confounding cannot be excluded.

DiMaggio *et al.*[44] initially reported an HR of 2.3 for the appearance of a developmental or behavioral disorder in children who underwent hernia repair before the age of 3 yr. In a follow-up study, using a sibling cohort to provide better control for confounders, they estimated that gender, age, medical history, socioeconomic factors, and the home environment accounted for nearly 50% of their initial estimated effect size. We included indices to account for these confounders in our model. Our results may differ from the results of DiMaggio *et al.*,[46] however, as we excluded children with a major developmental or intellectual disability (DD) diagnosed up to age 5 yr as the diagnosis may not be established until school entry and thus could significantly skew interpretation of earlier results.

Hansen *et al.*[47] suggest that pooled analysis of major and minor surgeries may not be appropriate due to the presence of significant confounders in children undergoing major surgery. Although we included neurosurgical cases, the small number is unlikely to account for the results obtained. Myringotomy cases (18% of total, but 33% of all cases in children 0 to 2 yr) were included as earlier concerns regarding an independent effect of middle ear effusions on language development have been refuted.[48,49] Moreover, if hearing problems and concern for future language/cognitive development were responsible for both myringotomy tube placement and subsequent deficits on EDI testing, then our results should have been biased toward greater effect in the younger age group. Alternatively, dental procedures under anesthesia made up 38% of our total surgical exposures but occurred predominantly in children 2 to 4 yr. Socially disadvantaged children are more likely to require these surgical interventions and are overrepresented in the study group overall. The lowest two income quintiles accounted for 49.7% of the total cohort. The significant impact of sociodemographic factors on EDI scores[15,50] underscores the concern that despite matching for sex and demographics and the inclusion of additional important socioeconomic covariates, residual confounding due to the combination of biological and social conditions that predispose this group of children to the requirement for surgery and anesthesia may underlie the negative neurodevelopmental results seen in the older children in the cohort.

Advantages of this study relate to the large population-based data set and uniform outcome measure derived from a single geographic area. The number of children exposed to GA in our study is comparable to the combined number of patients included in one previous meta-analysis. This is of particular relevance to the interpretation of outcomes after multiple GA exposures—for which we found no significantly increased risk over that of a single exposure.

Limitations include the risk of input error inherent in administrative data sets,[44,51] the lack of detailed information regarding specific anesthetic agents, doses and duration of exposure, and concern regarding the clinical relevance of the small differences in EDI results obtained. The EDI is administered across the entire public school system, but children enrolled in some private schools or schools operated by indigenous communities are not tested. The 15% loss of EDI results for all children enrolled in kindergarten in the test years in figure 1 may be accounted for by this subgroup, in addition to children who were absent from school on the test day or who had changed schools within the year. Although the EDI lacks the specificity of an individualized battery of neurocognitive tests, pertinent developmental domains are addressed in each child assessed by this instrument, and the population-level involvement provides data on a substantially greater number

of children than would be possible with an individualized testing strategy. Importantly, EDI results predict of future academic performance.[24] Brinkman *et al.*[20] report that "vulnerability" determined by EDI testing in kindergarten (scores less than 10 percentile) predicts scores "below expectation" on subsequent national standardized tests of literacy and numeracy in grades 3, 5, and 7. The strongest Spearman correlations were found with the language/cognition and communication/general knowledge domains, those found to be most affected in the current study. These results were confirmed using standardized assessments in grade 3[23] and grade 4.[21,22] On an individual level, the impact of a small decrease in performance in any EDI domain, as shown in the current study, would be difficult to establish. On a population level, however, a small difference, equivalent to an effect size of 0.2 SD in EDI scores in millions of children who undergo GA/surgery, may have significant population-based performance implications.

Conclusion

With a large cohort of children, we provide evidence that the association of GA exposure with subsequent neurocognitive deficits is dependent on the age of exposure. We are unable to demonstrate an independent association between GA exposure between birth and 2 years and EDI scores—the period of brain development previously suggested to conform to the period of greatest risk. Paradoxically, exposure to a single GA at a later stage of neurodevelopment, between 2 and 4 yr, was associated with small deficits, most significantly in communication/general knowledge and language/cognitive domains. Multiple exposures in this age period did not confer greater risk. These findings refute the previously held assumption that the earlier the GA exposure, the greater the likelihood of long-term neurocognitive risk. The results of the current study, in combination with the lack of negative neurocognitive outcomes recently reported in both the GAS (General Anesthesia Compared to Spinal Anesthesia)[10] and the PANDA (Pediatric Anesthesia and Neurodevelopment Assessment)[11] trials, increase the probability that residual or unknown confounding may be responsible for the greatest proportion of the negative neurocognitive effects seen in this older cohort of children.

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Competing Interests

The authors declare no competing interests.

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ANESTHESIOLOGY REFLECTIONS FROM THE WOOD LIBRARY-MUSEUM

From a Queen and from an Earl: Shakespearean "Black Blood" and Colton Gas

While administering 100% nitrous oxide to his Manhattan patients for just under a minute, dental anesthetist G. Q. Colton (1814 to 1898) routinely watched patients' complexions change with "Colton gas" from blue to black before dental extractions commenced. While hypothesizing that "overstimulation" by laughing gas led to death-like congestion, was Shakespearean scholar Colton reminded of quotes from two of the Bard's characters? In Shakespeare's narrative poem *The Rape of Lucrece*, Queen Hecuba's "blue blood changed to black in every vein." And in the Bard's *Henry VI*, the Earl of Warwick observed that the Duke's face was "black and full of blood." The scene (*above*, from *Chroniques d'Angleterre*) depicts England's Henry VI and his coronation as King of France. (Copyright © the American Society of Anesthesiologists' Wood Library-Museum of Anesthesiology.)

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