A Population-based Study Evaluating the Association between Surgery in Early Life and Child Development at Primary School Entry

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ABSTRACT

Background: It is unclear whether exposure to surgery in early life has long-term adverse effects on child development. The authors aimed to investigate whether surgery in early childhood is associated with adverse effects on child development measured at primary school entry.

Methods: The authors conducted a population-based cohort study in Ontario, Canada, by linking provincial health administrative databases to children's developmental outcomes measured by the Early Development Instrument (EDI). From a cohort of 188,557 children, 28,366 children who underwent surgery before EDI completion (age 5 to 6 yr) were matched to 55,910 unexposed children. The primary outcome was early developmental vulnerability, defined as any domain of the EDI in the lowest tenth percentile of the population. Subgroup analyses were performed based on age at first surgery (less than 2 and greater than or equal to 2 yr) and frequency of surgery.

Results: Early developmental vulnerability was increased in the exposed group (7,259/28,366; 25.6%) compared with the unexposed group (13,957/55,910; 25.0%), adjusted odds ratio, 1.05; 95% CI, 1.01 to 1.08. Children aged greater than or equal to 2 yr at the time of first surgery had increased odds of early developmental vulnerability compared with unexposed children (odds ratio, 1.05; 95% CI, 1.01 to 1.10), but children aged less than 2 yr at the time of first exposure were not at increased risk (odds ratio, 1.04; 95% CI, 0.98 to 1.10). There was no increase in odds of early developmental vulnerability with increasing frequency of exposure.

Conclusions: Children who undergo surgery before primary school age are at increased risk of early developmental vulnerability, but the magnitude of the difference between exposed and unexposed children is small. (ANESTHESIOLOGY 2016; 125:272-9)

SURGERY in childhood most often requires the administration of anesthetic or sedative medicines. There is substantial evidence that developing neurons are susceptible to injury induced by anesthesia or painful interventions in early life.[1,2] Anesthesia-related neurotoxicity has been reproduced in the nonhuman primate brain.[3,4] Furthermore, animal studies demonstrate long-term adverse changes in behavior, learning, and memory after anesthesia exposure in early life.[5–7]

Observational studies have found a variable association between anesthesia exposure in childhood and neurodevelopment, as assessed by academic performance indicators or select behavioral outcomes.[8–18] Despite this, pooled estimates

What We Already Know about This Topic

- The developing brain is susceptible to injury induced by anesthesia or painful interventions in early childhood
- Studies have found a variable association between anesthesia in early life and long-term neurodevelopment

What This Article Tells Us That Is New

- Children who undergo surgery before primary school age are at increased risk of early developmental vulnerability, but the magnitude of the risk is small
- Contrary to previous reports, age less than 2 yr at first exposure or multiple exposures to surgery did not increase the risk of adverse child development

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from these studies indicate at least a modest risk of impaired neurodevelopment after exposure to anesthesia and surgery in childhood.[19,20] Children at the highest risk of developmental problems after anesthesia exposure are aged less than 3 yr, corresponding with the period of increased neurodevelopment that peaks during early childhood.[21] However, these observational studies have major design limitations including the use of specialized populations (*e.g.*, Medicaid) or residual unmeasured confounding. Surgery, anesthesia, and concurrent illness can each contribute to adverse effects on child development. There are currently no studies of neurotoxicity associated with anesthesia or surgery that have utilized population-based measures of child development.

Despite this inconsistent evidence, there is increasing concern that anesthesia exposure in infants and toddlers has long-term adverse effects on behavior, learning, and memory.[22] Indeed, the collaborative public–private partnership between the U.S. Food and Drug Administration and International Anesthesia Research Society recently updated their consensus opinion statement to state that the risk of anesthesia in young children remains unclear and that better research is required to understand whether children are harmed from anesthesia exposure.[23] To inform parents, clinicians, and policymakers regarding this very important unresolved question, we undertook a population-based cohort study in Ontario, Canada, to investigate whether anesthesia and surgery in early childhood are associated with adverse effects on child development as measured using the Early Development Instrument (EDI), a validated population-based measure of child development.[24]

Materials and Methods

Overview

We identified exposure to surgery in childhood using population-based administrative databases at the Institute for Clinical Evaluative Sciences.[25] The developmental outcome measure was derived from the EDI,[24] housed at the Offord Centre for Child Studies, McMaster University, Hamilton, Ontario, Canada. The EDI is a population measure of child development at primary school entry (aged 5 to 6 yr). It was developed at the Offord Centre for Child Studies, McMaster University, and has since been implemented at a population level throughout most of Canada and also internationally (*e.g.*, the Australian Early Development Census).[26] It is a validated 103-item teacher-completed questionnaire used to assess children's readiness to engage in school activities in five major domains (physical health and well-being, social knowledge and competence, emotional health and maturity, language and cognitive development, and communication skills and general knowledge).[24] A complete description of the EDI development, domains, and validation data is available online from the Offord Centre for Child Studies.[27] Data collection for the EDI in Ontario was undertaken in all public and Catholic schools in three consecutive cycles between 2004 and 2012. Research ethics boards at The Hospital for Sick Children, Toronto, Ontario, Canada (#1000046454), and McMaster University (#14-532-C), approved the study (Trial Registration clinicaltrials.gov Identifier: NCT02595801).

Cohort Assembly

EDI and Institute for Clinical Evaluative Sciences databases were linked directly using three identifiers (date of birth, sex, and postal code). Excluded before database linkage were children with an incomplete EDI, those in junior kindergarten or not established in senior kindergarten (in class less than 1 month), those who had any physical disabilities recorded in the EDI, and those with missing identifiers. Other exclusions after database linkage were children not born in Canada (out-of-country exposure to surgery could not be determined) and children with potential healthcare-related causes of impaired child development (*e.g.*, a history of fetal intervention, radiation therapy, brachytherapy, pharmacotherapy, or chemotherapy, and those followed by a cardiology or cardiovascular service). In addition, children who had a diagnosis of behavioral, learning, or developmental problems recorded in the EDI were excluded, given that these children can have age-dependent variations in brain anatomy, function, and connectivity,[28] which may alter their sensitivity to the potential neurotoxic effects of anesthetic and sedative drugs.

We determined whether an individual was exposed to any eligible surgical procedure during the time period from birth to date of EDI completion. Procedure types were identified using either Canadian Classification of Health Interventions therapeutic intervention codes or Canadian Classification of Diagnostic, Therapeutic, and Surgical Procedures codes, according to the standard used at the time of exposure (Supplemental Digital Content 1, http://links.lww.com/ALN/B292). All surgical procedures identified within this time window were documented; furthermore, participants were characterized according to their age at first surgery, number of surgical procedures, and cumulative length of hospital stay.

Outcomes

The primary outcome was early developmental vulnerability, defined as any major domain of the EDI in the lowest tenth percentile of a population.[29] The percentile definition for this outcome measure was chosen by EDI researchers to identify vulnerable children who will likely benefit from population-level interventions but who may not meet individual diagnostic criteria for developmental delay.[30] This outcome measure has subsequently been shown to have strong predictive validity for future academic achievement,[31] has been used to assess the prevalence of mental health problems in children,[32] and can discriminate the effect of other early life experiences and disease states (gestational diabetes, anemia of pregnancy, and gestational age at birth) on child development.[33–35]

Secondary outcomes were performance in major EDI domains and the multiple challenge index, defined as vulnerability in greater than or equal to 9 subdomains of the EDI.[36] Normative data for the Ontario population were determined using the first (2004 to 2006) cycle of the EDI.[27]

Covariates

Individuals in the cohort were characterized with respect to demographics (aboriginal status, age category [less than 2 and greater than or equal to 2 yr] at the time of first surgery, median neighborhood household income quintile, rurality of residence, and sex), birth characteristics (gestational age at birth, mother's age at birth, multiple births, and year and quarter of birth), and surgical admission characteristics (cumulative length of hospital stay and type of surgery).

Matching and Statistical Analysis

We used both matching and regression techniques to adjust for confounding in the association between surgery exposure and early developmental vulnerability. An exact matching technique was chosen for this large population-based cohort to allow the use of a multiple matching ratio (1:2) to decrease variance in the matched sample size without increasing risk of bias in matched pairs.[37] Initially, children who underwent surgery were matched exactly to individuals who were not exposed to surgery on five important confounders: gestational age (in weeks) at birth, mother's age at birth (categorized as less than 18, 18 to 23, 24 to 29, 30 to 34, and greater than 35 yr), rurality of residence, sex, and year and quarter of birth. The matched cohort was then characterized using standard descriptive statistics. Estimates of effect are reported as standardized mean difference or absolute risk difference as appropriate. Unadjusted differences in outcomes between the matched groups were tested using a paired Student's t test or McNemar test as appropriate. Multivariable conditional logistic regression was then used to determine the adjusted association between exposure to surgery (independent variable) and the primary (early developmental vulnerability) and secondary (performance in specific EDI domains, and multiple challenge index) outcomes. A conditional maximum likelihood approach to regression analysis was used to avoid overestimation of odds ratios (ORs) with matched data. Covariates (aboriginal status, age category, and median household income quintile) adjusted for in the models were specified *a priori*. Adjusted associations are presented as OR and 95% CIs. Statistical significance was defined as two-tailed $P < 0.05$. All analyses were performed using SAS 9.4 (SAS Institute, USA).

Results

We identified 374,577 children in Ontario, Canada, with a completed EDI. Of these, 317,169 children were eligible for database linkage, and 259,247 (82%) were linked to unique records in administrative healthcare databases. The characteristics of those children not linked to RPDB are presented in Supplemental Digital Content 2 (http://links.lww.com/ALN/B293). Of those individuals in the linked cohort, 188,557 met the study eligibility criteria. We then exactly matched 28,366 children who underwent surgery to 55,910 children who did not undergo any surgery (fig. 1).

The mean (SD) age at EDI completion was 5.7 (0.3) yr. The characteristics of the matched cohort are summarized in table 1. Surgical procedures performed (n greater than 50) for children included in the cohort are summarized in Supplemental Digital Content 3 (http://links.lww.com/ALN/B294). The most common surgical procedures performed were implantation of an internal device in the tympanic membrane (myringotomy and tube placement; n = 6,346), excision of tonsils and adenoids/tonsillectomy (n = 5,856), circumcision (outside of newborn period; n = 2,740), and repair of muscles of the chest and abdomen (open approach to hernia repair; n = 1,354).

Unadjusted Association of Surgery with Child Development in the Matched Cohort

The proportion of children demonstrating early developmental vulnerability (any major EDI domain in the lowest tenth percentile of the population) in the exposed and unexposed groups was 25.6% (7,259/28,366) and 25.0% (13,957/55,910), respectively ($P = 0.047$; table 2). There was no consistent trend for reduced performance in specific domains of the EDI; there was no difference between groups in the proportion of children with a multiple challenge index ($P = 0.31$; table 2).

Adjusted Association of Surgery with Child Development

There was a statistically significant increase in the adjusted odds of early developmental vulnerability in children exposed to surgery (OR, 1.05; 95% CI, 1.01 to 1.08; $P = 0.009$). When the analysis was repeated after excluding children who underwent surgery for myringotomy and tube placement, the small increase observed in the adjusted odds of the primary outcome was unchanged (OR, 1.05; 95% CI, 1.01 to 1.09; $P = 0.03$). Differences in the performance in specific EDI domains were not consistent in direction, and there was no difference in adjusted odds of a multiple challenge index (table 3).

Subgroup Analyses

The adjusted odds of early developmental vulnerability was similar in the exposed and unexposed groups for children aged less than 2 yr at the time of first exposure (table 3). For children aged greater than or equal to 2 yr at the time of first exposure, there was a small increase in the adjusted odds of early developmental vulnerability in the exposed group compared with the unexposed group (table 3). Similar results were found for the multiple challenge index (table 3).

We found no evidence that increasing frequency of exposure to surgery was related to the adjusted odds of early developmental vulnerability. Adjusted odds ratios for each exposure group were similar (range, 1.04 to 1.06; fig. 2).

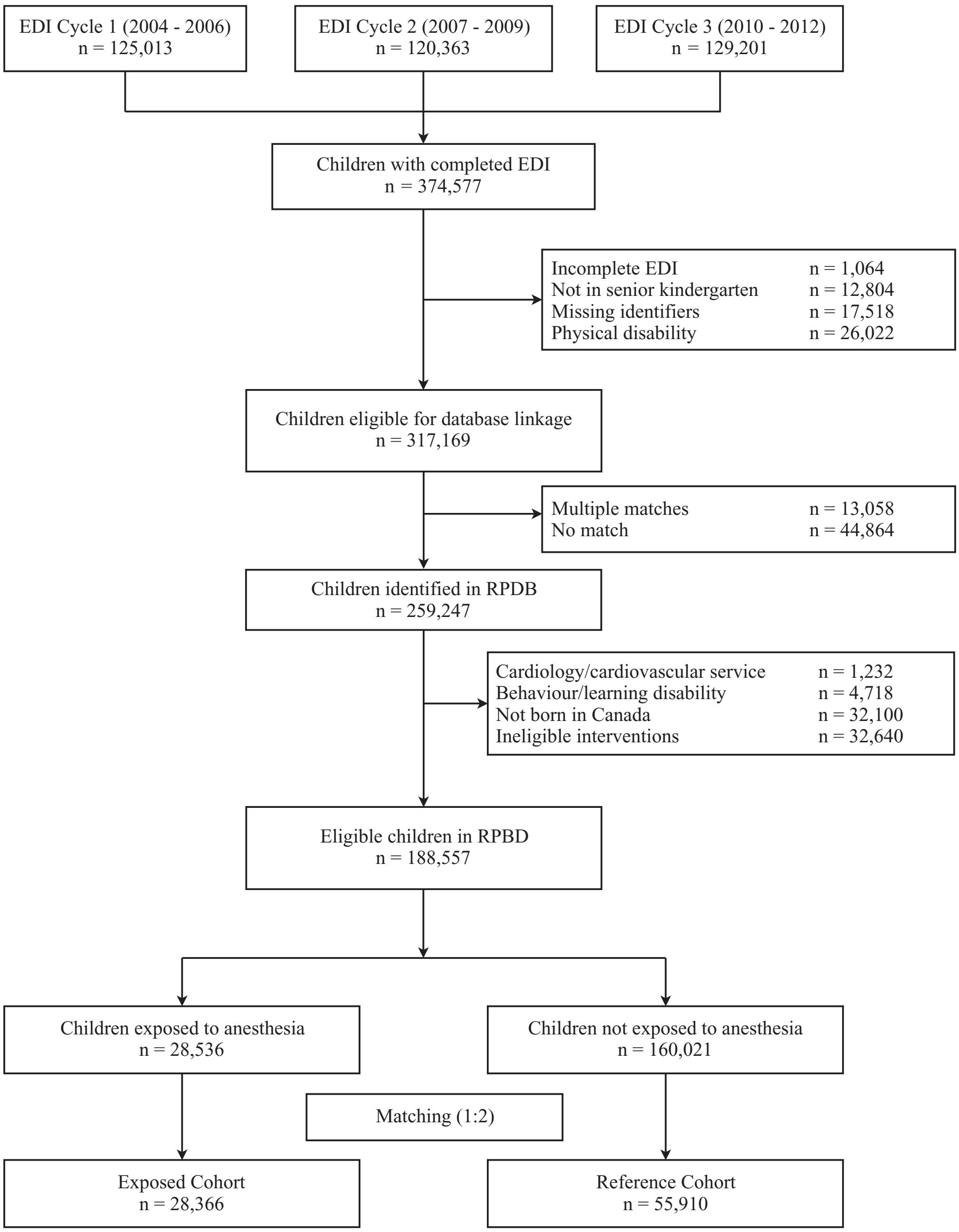

Fig. 1. Flow diagram. EDI = Early Development Instrument; RPDB = Registered Persons Database.

To minimize potential confounding from hospitalization and concurrent illness, we measured outcomes in children after a single surgery with a cumulative length of hospital stay less than 2 days. In this subgroup, the difference in the adjusted odds of early developmental vulnerability (OR, 1.04; 95% CI, 1.00 to 1.08; *P* = 0.08; fig. 2) or having a multiple challenge index (OR, 1.11; 95% CI, 1.00 to 1.24; *P* = 0.06) was not statistically significant.

Discussion

In a matched cohort of 84,276 children in Ontario, we found a small increase in the unadjusted rate of early developmental vulnerability (any major EDI domain in the lowest tenth percentile of the population), comparing children exposed and unexposed to surgery. The increase in adjusted odds in the exposed group was statistically significant, but the magnitude of the difference was small.[38] Age less than 2 yr at first exposure and multiple exposures to surgery were not risk factors for adverse developmental outcomes.

Although development of brain structures continue throughout childhood,[39] there is an important period of structural and functional brain development in early life that has implications for cognition, language, and social

Table 1. Characteristics of the Exposed and Unexposed Groups in the Matched Cohort

Characteristic	Cohort Groups	
	No Surgery (n = 55,910)	Surgery (n = 28,366)
Age at EDI completion (yr), mean(SD)	5.70 ± 0.29	5.70 ± 0.30
Female, N (%)	20,559 (36.8)	10,305 (36.3)
Gestational age weeks at delivery (wk)	39.02 ± 1.48	38.99 ± 1.54
Multiple births, N (%)	563 (1.0)	280 (1.0)
Neighborhood income quintile, N (%)		
1	9,270 (16.6)	4,357 (15.4)
2	10,361 (18.5)	5,024 (17.7)
3	11,989 (21.4)	6,078 (21.4)
4	12,945 (23.2)	6,934 (24.4)
5	11,235 (20.1)	5,917 (20.9)
Unknown	110 (0.2)	56 (0.2)
Aboriginal, N (%)	567 (1.0)	267 (1.0)
Home location, N (%)		
Urban	49,663 (88.8)	25,108 (88.5)
Rural	6,218 (11.1)	3,238 (11.4)
Unknown	29 (0.1)	20 (0.1)
Number of surgery exposure(s), N (%)		
0	55,910 (100.0)	
1	0 (0.0)	22,812 (80.4)
2	0 (0.0)	4,167 (14.7)
3	0 (0.0)	1,008 (3.6)
≥ 4	0 (0.0)	379 (1.3)
Age at time of first surgery exposure, N (%)		
< 2 yr	0 (0.0)	10,937 (38.6)
≥ 2 yr	0 (0.0)	17,429 (61.4)
Cumulative length of stay (d), Median (IQR)	0 (0)	1(1–2)

EDI = Early Development Instrument; IQR = interquartile range.

behavior.[40,41] Investigators have hypothesized that children have an increased risk of adverse developmental outcomes when exposed to anesthesia and surgery during this period of increased neurodevelopment.[2,42] We used a conservative age limit of less than 2 yr to define the period of increased neurodevelopment. Our findings suggest that exposure to anesthesia and surgery before this age limit does not adversely affect child development. The neurotoxicity of general anesthetic drugs is also known to be dose-dependent.[43] As in previous studies,[12,13] we used frequency of exposure to anesthesia and surgery as a surrogate for cumulative dose. The absence of any dose–response (range of odds ratios, 1.04 to 1.06) in our study indicates that adverse child development is likely independent of cumulative exposure to anesthesia and surgery in early life. Overall, our findings strongly suggest that anesthesia-related neurotoxicity is not a strong causative pathway for adverse developmental outcomes in childhood.

Our findings are inconsistent with pooled estimates from other observational studies.[19,20] These differences may be due to several factors, including the characteristics of populations (*e.g.*, Medicaid) and types of surgery studied. To ensure that our results were not confounded by anesthesia and surgery of short duration, we also analyzed outcome data after excluding surgery for myringotomy and tube placement, which is typically a surgery of short duration. Notably, these findings support the recently published interim results from the GAS Study consortium; in a prospective randomized controlled equivalence trial, these investigators found no evidence that a general anesthesia lasting less than 1 hr in a cohort of 294 infants increased the risk of adverse neurodevelopmental outcomes at 2 yr of age compared with regional anesthesia only.[42]

The outcome measure used in clinical studies of neurotoxicity can influence the ability to detect developmental deficits.[44] To our knowledge, there are no direct neurodevelopmental tests that are administered on a population level and are available for research purposes. To overcome this limitation, outcome measures in previous studies include academic performance[8,13,14,17] and diagnoses of behavioral disorders[9,12,18] or learning disability.[11,13,17] The EDI is a validated population-based measure of child development and demonstrates high levels of reliability.[24,45] Individual domains that contribute to the EDI can reliably distinguish between children of different levels of ability,[46] and the EDI has moderate concurrent validity with direct measures of child development.[24] It correlates with similar domains in the FirstSTEP Screening Test for Evaluating Preschoolers (0.65, social competence; 0.73, emotional maturity; 0.58, language and cognitive development), Peabody Picture Vocabulary Test (0.57, communication skills and general knowledge), and Who Am I? (0.46, language and cognitive development) tools.[24] Notably, the Australian Early Development Index, which uses the same overall content and structure as the EDI, has a predominantly moderate to strong correlation with similar developmental outcomes.[26]

The current study has several important strengths and limitations. It is the largest population-based cohort study undertaken, investigating the effects of anesthesia and surgery in early life on child development. The large sample size offers core methodological strengths, including statistical power to detect small effect differences and the ability to directly reduce imbalance in confounders between groups by matching simultaneously on multiple covariates, in contrast to multivariate matching using propensity scores.[47] As in any observational research, limitations include an inability to infer causality, difficulty in differentiating between the effects of potential confounding factors, and the presence of residual confounding from unmeasured covariates. However, in our study, the use of population-based health administrative and demographic databases allowed us to directly match groups using multiple covariates, including socioeconomic and geographical factors, reducing the potential for

Table 2. Unadjusted Early Development Instrument Domain Scores and Vulnerability in Exposed and Unexposed Groups in the Matched Cohort

	Cohort Groups			
Outcomes	No Surgery (n = 55,910)	Surgery (n = 28,366)	SMD or ARD	*P* Value
EDI domain scores, mean (SD)				
Physical health and well-being	8.96 ± 1.21	8.92 ± 1.23	−0.03	< 0.001
Social knowledge and competence	8.44 ± 1.71	8.38 ± 1.73	−0.04	< 0.001
Emotional health and maturity	8.13 ± 1.43	8.09 ± 1.46	−0.03	< 0.001
Language and cognitive development	8.77 ± 1.57	8.77 ± 1.57	0.00	0.58
Communication skills and general knowledge	7.97 ± 2.36	8.00 ± 2.32	0.01	0.06
Early developmental vulnerability, N (%)	13,957 (25.0)	7,259 (25.6)	0.6	0.047
Multiple challenge index, N (%)	1,453 (2.6)	771 (2.7)	0.1	0.31
EDI domains ≤ tenth percentile, N (%)				
Physical health and well-being	6,568 (11.7)	3,546 (12.5)	0.7	0.003
Social knowledge and competence	4,505 (8.1)	2,367 (8.3)	0.2	0.36
Emotional health and maturity	5,162 (9.2)	2,898 (10.2)	1.0	< 0.001
Language and cognitive development	4,023 (7.2)	2,004 (7.1)	−0.1	0.009
Communication skills and general knowledge	5,303 (9.5)	2,514 (8.9)	−0.6	0.01

ARD = absolute risk difference; EDI = Early Development Instrument; SMD = standardized mean difference.

Table 3. Adjusted Odds of Vulnerability for Children Exposed to Surgery Compared with Children Not Exposed to Surgery, Stratified According to Age at the Time of First Surgery

	Age at First Exposure					
	Any Age (n = 28,366)		< 2 yr (n = 10,937)		≥ 2 yr (n = 17,429)	
Outcomes	OR (95% CI)	*P* Value	OR (95% CI)	*P* Value	OR (95% CI)	*P* Value
Early developmental vulnerability	1.05 (1.01–1.08)	0.009	1.04 (0.98–1.10)	0.19	1.05 (1.01–1.10)	0.02
Multiple Challenge Index	1.06 (0.97–1.16)	0.18	0.94 (0.82–1.09)	0.42	1.15 (1.03–1.29)	0.02
EDI domains ≤ tenth percentile:						
Physical health and well-being	1.09 (1.04–1.14)	< 0.001	1.09 (1.01–1.17)	0.02	1.09 (1.03–1.15)	0.004
Social knowledge and competence	1.05 (1.00–1.11)	0.07	1.02 (0.93–1.11)	0.72	1.08 (1.00–1.15)	0.04
Emotional health and maturity	1.13 (1.07–1.18)	< 0.001	1.13 (1.04–1.22)	0.003	1.13 (1.06–1.20)	< 0.001
Language and cognitive development	0.99 (0.94–1.05)	0.79	0.92 (0.84–1.01)	0.07	1.04 (0.97–1.12)	0.25
Communication skills and general knowledge	0.94 (0.89–0.99)	0.01	0.88 (0.81–0.96)	0.003	0.98 (0.91–1.04)	0.45

EDI = Early Development Instrument; OR = odds ratio.

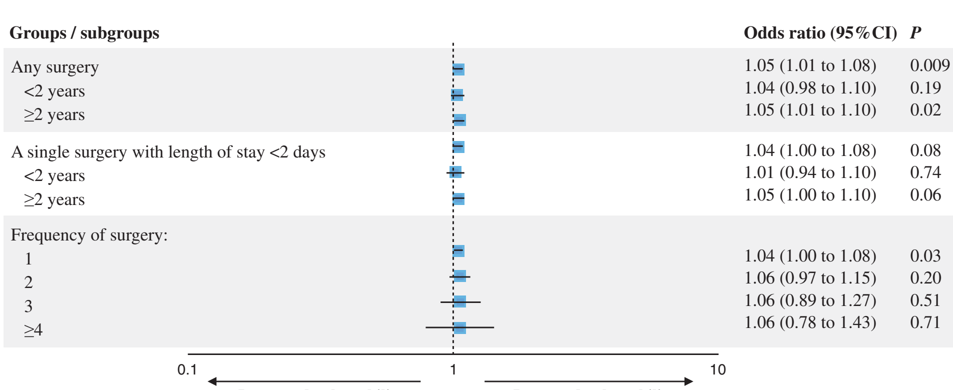

Fig. 2. Adjusted odds ratios of early development vulnerability for children who underwent any surgery stratified according to age at the time of first surgery, a single surgery with an associated length of stay less than 2 days stratified according to age, and by frequency of surgery.

unmeasured confounding. Second, *a priori* we excluded children with known behavioral, learning, and developmental disability from the cohort. These children can have age-dependent variations in brain anatomy, function, and connectivity,[28] which may alter their sensitivity to the potential neurotoxic effects of anesthetic and sedative drugs. In addition, there is a tendency for increased use of healthcare services by some of these children (*e.g.*, autism spectrum disorder),[48] which we anticipated would introduce a significant risk of sampling bias in the measured association between anesthesia and surgery exposure and developmental vulnerability. As a result, our findings cannot be extrapolated to children in these populations, and we suggest that population-specific estimates of risk need to be determined separately for these children. Third, while we excluded children with physical and developmental disabilities, the study design has an inherent bias for worse developmental outcomes in the exposed group due to confounding from underlying health problems. However, we found little difference in outcomes between groups.

In conclusion, this population-based study found that children who undergo surgery before primary school age are at increased risk of early developmental vulnerability, but the magnitude of the difference between exposed and unexposed children is small. Age less than 2 yr at first exposure and multiple exposures to surgery were not risk factors for adverse developmental outcomes.

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Competing Interests

The authors declare no competing interests.

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